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(54) **Title:** DOSAGE FORM THAT IS SAFEGUARDED FROM ABUSE

(57) **Abstract:** The present invention relates to a dosage form that is safeguarded from abuse. In addition to one or more active ingredients that could be potentially subject to abuse, said dosage form comprises two or more of the following constituents (a)-(d): (a) at least one substance that irritates the nasal and/or pharyngeal region; (b) at least one agent that increases the viscosity, which forms a gel in an extract that is obtained from the dosage form with the aid of a required minimum quantity of an aqueous liquid, wherein the said gel can still be visibly distinguished after being introduced into an additional quantity of an aqueous liquid, (c) at least one antagonist for the active ingredient or ingredients that can be potentially subject to abuse, and (d) at least one emetic.

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Dosage Form That is Safeguarded from Abuse

The present invention pertains to a dosage form that is safeguarded from abuse, which contains, in addition to one or more active ingredients that could be potentially subject to abuse, two or more of the following components a)-d):

(a) at least one substance irritating the nasal and/or pharyngeal region,

(b) at least one agent that increases the viscosity, which forms a gel in an extract obtained from the dosage form with the aid of a required minimum quantity of an aqueous liquid, wherein the said gel continues to be able to be visually distinguished after being introduced
into an additional quantity of an aqueous liquid,

(c) at least one antagonist for the active ingredient or the active ingredients that could be potentially subject to abuse, and

(d) at least one emetic.

A plurality of pharmaceutical active ingredients also have a potential for abuse besides an excellent efficacy in their particular field of application, i.e., they may be used by an abuser in order to bring about effects that do not correspond to the intended medical purpose of these active ingredients.

For example, opiates, which have excellent efficacy in the control of intense to very intense pain, are frequently used by abusers to achieve intoxicating, euphoric states.

Oral dosage forms, which contain such active ingredients with a potential for abuse, do not usually lead to the result desired by the abuser even when large quantities are ingested in an abusive manner, because the concentrations of the active ingredients build up in the blood only slowly. To nevertheless make abuse possible, the corresponding dosage forms are comminuted by the abuser, e.g., in a mortar, and applied, e.g., by sniffing via the nose. In another form of abuse, the active ingredient is extracted from the powder obtained by comminuting the dosage form by means of a preferably aqueous liquid, and the resulting solution is administered parenterally, especially intravenously, optionally after filtration through cotton or cellulose. The concentration of the active ingredient builds up in an accelerated manner in these forms of administration compared with the oral administration, with the result desired by the abuser.

The object of the present invention was therefore to make available a dosage form for active ingredients that could be potentially subject to abuse, which guarantees its therapeutic action in case of use as intended, but does not exert the action desired by the abuser in case of abusive ingestion.

This object is accomplished by the dosage form safeguarded from abuse according to the present invention, which contains, in addition to one or more active ingredients that could be potentially subject to abuse, two or more of the following components a)-d):

(a) at least one substance irritating the nasal and/or pharyngeal region,

(b) at least one agent that increases the viscosity, which forms a gel in an extract obtained from the dosage form with the aid of a required minimum quantity of an aqueous liquid, wherein the said gel continues to be able to be visually distinguished after being introduced into an additional quantity of an aqueous liquid,

(c) at least one antagonist for the active ingredient or the active ingredients that could be potentially subject to abuse, and

(d) at least one emetic.

The components (a) through (d) are each already suitable in themselves for safeguarding the dosage form from abuse. Thus, component (a) is preferably suitable for safeguarding the dosage form from nasal and/or parenteral abuse; component (b) is preferably suitable for use against parenteral abuse; component (c) is preferably suitable against nasal and/or parenteral abuse, and component (d) is preferably suitable against parenteral and/or oral and/or nasal abuse. Due to the combination of at least two of these above-mentioned components according to the present invention, it is possible to safeguard the dosage form according to the present invention against abuse even more effectively.

In one embodiment, the dosage form according to the present invention contains three of the components (a)-(d) in the abuse combination, preferably (a), (b) and (c) or (a), (b) and (d).

In another embodiment, the dosage form according to the present invention contains all the components (a)-(d).

Pharmaceutical active ingredients with a potential for abuse, as well as the quantities to be used and the methods for producing same are known per se to the person skilled in the art and they may be present as such in the dosage form according to the present invention in the form of corresponding, physiologically compatible compounds, especially in the form of their salts or solvates.

A combination of two or three of the components (a), (b) and (d) is especially suitable for preventing the abuse of a pharmaceutical active ingredient, which is selected from the group comprising opiates, opioids, tranquilizers, preferably benzodiazepines, stimulants, and other narcotics.

A combination of two or three of the components (a), (b) and (d) is especially suitable for preventing the abuse of opiates, opioids, tranquilizers as well as other narcotics, which are selected from the group comprising *N*-{1-[2-(4-ethyl-5-oxo-2-tetrazolin-1-yl)-ethyl]-4-methoxymethyl-4-piperidyl} propionanilide (alfentanil), 5,5-diallyl barbituric acid (allobarbital),

allylprodine, alpha-prodine, 8-chloro-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-a][1,4]-benzodiazepine (alprazolam), 2-diethylaminopropiophenone (amfepramone), (±)-α-methyl phenethylamine (amphetamine), 2-(α-methylphenethyl-amino)-2-phenyl acetonitrile (amphetaminil), 5-ethyl-5-isopentyl barbituric acid (amobarbital), anileridine, apocodeine, 5,5-diethyl barbituric acid (barbital), benzylmorphine, bezitramide, 7-bromo-5-(2-pyridyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (bromazepam), 2-bromo-4-(2-chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]-triazolo[4,3-a][1,4]diazepine (brotizolam), 17-cyclopropylmethyl-4,5α-epoxy-7α[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6-methoxy-6,14-*endo*-ethanomorphinan-3-ol (buprenorphine), 5-butyl-5-ethyl barbituric acid (butobarbital), butorphanol, (7-chloro-1,3-dihydro-1-methyl-2-oxo-5-phenyl-2*H*-1,4-benzodiazepin-3-yl)-dimethyl carbamate (camazepam), (1*S*,2*S*)-2-amino-1-phenyl-1-propanol (cathine/D-norpseudoephedrine), 7-chloro-*N*-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2-ylamine-4 oxide (chlordiazepoxide), 7-chloro-1-methyl-5-phenyl-1*H*-1,5-benzodiazepine-2,4(3*H*,5*H*)-dione (clobazam), 5-(2-chlorophenyl)-7-nitro-1*H*-1,4-benzodiazepin-2(3*H*)-one (clonazepam), clonitazene, 7-chloro-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-3-carboxylic acid (clorazepate), 5-(2-chlorophenyl)-7-ethyl-1-methyl-1*H*-thieno[2,3-e][1,4]-diazepin-2(3*H*)-one (clotiazepam), 10-chloro-11b-(2-chlorophenyl)-2,3,7,11b-tetrahydrooxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one (cloxazolam), (-)-methyl-[3β-benzoyloxy-2β(1αH,5α*H*)-tropane carboxylate (cocaine), 4,5α-epoxy-3-methoxy-17-methyl-7-morphinen-6α-ol (codeine), 5-(1-cyclohexenyl)-5-ethyl barbituric acid (cyclobarbital), cyclorphan, cyprenorphine, 7-chloro-5-(2-chlorophenyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (delorazepam), desomorphine, dextromoramide, (+)-(1-benzyl-3-dimethylamino-2-methyl-1-phenylpropyl) propionate (dextropropoxyphene), dezocine, diampromide, diamorphone, 7-chloro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (diazepam), 4,5α-epoxy-3-methoxy-17-methyl-6α-morphinanol (dihydrocodeine), 4,5α-epoxy-17-methyl-3,6a-morphinandiol (dihydromorphine), dimenoxadol, dimephetamol [sic - Tr.Ed.], dimethyl thiambutene, dioxaphetyl butyrate, dipipanone, (6a*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[c]chromen-1-ol (dronabinol), eptazocine, 8-chloro-6-phenyl-4*H*-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine (estazolam), ethoheptazine, ethyl methyl thiambutene, ethyl-[7-chloro-5-(2-fluorophenyl)-2,3-dihydro-2-oxo-1*H*-1,4-benzodiazepin-3-carboxylate] (ethyl loflazepate), 4,5α-epoxy-3-ethoxy-17-methyl-7-morphinen-6α-ol (ethylmorphine), etonitrazene, 4,5α-epoxy-7α-(1-hydroxy-1-methylbutyl)-6-methoxy-17-methyl-6,14-*endo*-etheno-morphinan-3-ol (etorphine), *N*-ethyl-3-phenyl-8,9,10-trinorbornan-2-ylamine (fencamfamine), 7-[2-(α-methylphenethylamino)-ethyl] theophylline (fenethylline), 3-(α-methylphenethylamino) propionitrile (fenproporex), *N*-(1-phenethyl-4-piperidyl) propionanilide (fentanyl), 7-chloro-5-(2-fluorophenyl)-1-methyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (fludiazepam), 5-(2-fluorophenyl)-1-methyl-7-nitro-1*H*-1,4-benzodiazepin-2-(3*H*)-one (flunitrazepam), 7-chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (flurazepam), 7-chloro-5-phenyl-1-(2,2,2-trifluoroethyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (halazepam), 10-bromo-11b-(2-fluorophenyl)-2,3,7,11b-tetrahydro[1,3]oxazolo[3,2-d][1,4]benzodiazepin-6(5*H*)-one (haloxazolam), heroin, 4,5α-epoxy-3-methoxy-17-methyl-6-morphinanone (hydrocodone), 4,5α-epoxy-3-hydroxy-17-methyl-6-morphinanone (hydromorphone), hydroxypethidine, isomethadone, hydroxymethyl morphinan, 11-chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4*H*-[1,3]oxazino[3,2-d][1,4]benzodiazepin-4,7(6*H*)-dione (ketazolam), 1-[4-(3-hydroxyphenyl)-1-methyl-4-piperidyl]-1-propanone (ketobemidone), (3*S*,6*S*)-6-dimethylamino-4,4-diphenylheptan-3-yl acetate (levacetylmethadol (LAAM)), (-)-6-dimethylamino-4,4-diphenyl-3-heptanone (levomethadone), (-)-17-methyl-3-morphinanol (levorphanol), levophenacyl morphan, lofentanil, 6-(2-chlorophenyl)-2-(4-methyl-1-piperazinylmethylene)-8-nitro-2*H*-imidazo[1,2a][1,4]benzodiazepin-1(4*H*)-one (loprazolam), 7-chloro-5-(2-chlorophenyl)-3-hydroxy-1*H*-1,4-benzodiazepin-2(3*H*)-one (lorazepam), 7-chloro-5-

(2-chlorophenyl)-3-hydroxy-1-methyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (lormetazepam), 5-(4-chlorophenyl)-2,5-dihydro-3*H*-imidazo[2,1-*a*]isoindol-5-ol (mazindol), 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (medazepam), *N*-(3-chloropropyl)-α-methylphenetylamine (mefenorex), meperidine, 2-methyl-2-propyl trimethylene dicarbamate (meprobamate), meptazinol, metazocine, methylmorphine, *N*,α-dimethylphenethylamine (methamphetamine), (±)-6-dimethylamino-4,4-diphenyl-3-heptanone (methadone), 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone (methaqualone), methyl-[2-phenyl-2-(2-piperidyl)acetate] (methyl phenidate), 5-ethyl-1-methyl-5-phenyl barbituric acid (methyl phenobarbital), 3,3-diethyl-5-methyl-2,4-piperidinedione (methyprylon), metopon, 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (midazolam), 2-(benzhydrylsulfinyl) acetamide (modafinil), 4,5α-epoxy-17-methyl-7-morphinene-3,6α-diol (morphine), myrophine, (±)-*trans*-3-(1,1-dimethylheptyl)-7,8,10,10α-tetrahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran-9(6α*H*)-one (nabilone), nalbuphen, nalorphine, narceine, nicomorphine, 1-methyl-7-nitro-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (nimetazepam), 7-nitro-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (nitrazepam), 7-chloro-5-phenyl-1*H*-1,4-benzodiazepin-2-(3*H*)-one (nordazepam), norlevorphanol, 6-dimethylamino-4,4-diphenyl-3-hexanone (normethadone), normorphine, norpipanone, the coagulated juice of the plants belonging to the species *Papaver somniferum* (opium), 7-chloro-3-hydroxy-5-phenyl-1*H*-1,4-benzodiazepin-2-(3*H*)-one (oxazepam), (*cis-trans*)-10-chloro-2,3,7,11b-tetrahydro-2-methyl-11b-phenyloxazolo[3,2-*d*][1,4]benzodiazepin-6-(5*H*)-one (oxazolam), 4,5α-epoxy-14-hydroxy-3-methoxy-17-methyl-6-morphinanone (oxycodone), oxymorphone, plants and plant parts of the plants belonging to the species *Papaver somniferum* (including the subspecies *setigerum*) (*Papaver somniferum*), papaveretum, 2-imino-5-phenyl-4-oxazolidinone (pernoline), 1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol (pentazocine), 5-ethyl-5-(1-methylbutyl) barbituric acid (pentobarbital), ethyl-(1-methyl-4-phenyl-4-piperidine-carboxylate) (pethidine), phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, pholcodeine, 3-methyl-2-phenyl morpholine (phenmetrazine), 5-ethyl-5-phenyl barbituric acid (phenobarbital), α,α-dimethyl phenethylamine (phentermine), 7-chloro-5-phenyl-1-(2-propinyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (pinazepam), α-(2-piperidyl)benzhydryl alcohol (pipradol), 1'-(3-cyano-3,3-diphenylpropyl)[1,4'-bipiperidine]-4'-carboxamide (piritramide), 7-chloro-1-(cyclopropylmethyl)-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (prazepam), profadol, proheptazine, promedol, properidine, propoxyphene, *N*-(1-methyl-2-piperidinoethyl)-*N*-(2-pyridyl) propionamide, methyl-{3-[4-methoxycarbonyl-4-(*N*-phenylpropaneamido)piperidino]propanoate} (remifentanil), 5-*sec.*-butyl-5-ethyl barbituric acid (secbutabarbital), 5-allyl-5-(1-methylbutyl) barbituric acid (secobarbital), *N*-{4-methoxymethyl-1-[2-(2-thienyl)ethyl]-4-piperidyl} propionanilide (sufentanil), 7-chloro-2-hydroxy-methyl-5-phenyl-1*H*-1,4-benzodiazepin-2-(3*H*)-one (temazepam), 7-chloro-5-(1-cyclohexenyl)-1-methyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (tetrazepam), ethyl-(2-dimethylamino-1-phenyl-3-cyclohexane-1-carboxylate) (tilidine (*cis* and *trans*)), tramadol, 8-chloro-6-(2-chlorophenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine (triazolam), 5-(1-methylbutyl)-5-vinyl barbituric acid (vinylbital), (1R*,2R*)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl) phenol, (1R,2R,4S)-2-[dimethylamino)methyl-4-(*p*-fluorobenzyloxy)-1-(*m*-methoxyphenyl) cyclohexanol, each optionally in the form of corresponding stereoisomeric compounds as well as corresponding derivatives, especially esters or ethers, and all being physiologically compatible compounds, especially salts and solvates.

If the combination for safeguarding from abuse comprises the safeguarding by component (c), it is especially suitable for preventing the abuse of a pharmaceutical active ingredient that is selected from the group comprising opiates, opioids, stimulants and other narcotics.

Especially suitable is a combination containing component (c) for preventing the abuse of opiates, opioids as well as other narcotics, which are selected from the group comprising *N*-{1-[2-(4-ethyl-5-oxo-2-tetrazolin-1-yl)ethyl]-4-methoxymethyl-4-piperidyl} propionanilide (alfentanil), allylprodine, alpha-prodine, 2-diethylaminopropiophenone (amfepramone), (±)-α-methyl phenethylamine (amphetamine), 2-(α-methylphenethylamino)-2-phenyl acetonitrile (amphetaminil), anileridine, apocodeine, benzylmorphine, bezitramide, 17-cyclopropylmethyl-4,5α-epoxy-7α[(S)-1-hydroxy-1,2,2-trimethyl-propyl]-6-methoxy-6,14-*endo*-ethanomorphinan-3-ol (buprenorphine), butorphanol, (1*S*,2*S*)-2-amino-1-phenyl-1-propanol (cathine/D-norpseudoephedrine), clonitazene, (-)-methyl-[3β-benzoyloxy-2β(1αH,5α*H*)-propane-carboxylate] (cocaine), 4,5α-epoxy-3-methoxy-17-methyl-7-morphinen-6α-ol (codeine), cyclorphan, cyprenorphine, desmorphine, dextromoramide, (+)-(1-benzyl-3-dimethylamino-2-methyl-1-phenylpropyl) propionate (dextropropoxyphene), dezocine, diampromide, diamorphone, 4,5α-epoxy-3-methoxy-17-methyl-6α-morphinanol (dihydrocodeine), 4,5α-epoxy-17-methyl-3,6a-morphinandiol (dihydromorphine), dimenoxadol, dimephetamol, dimethyl thiambutene, dioxaphetyl butyrate, dipipanone, (6a*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[c]chromen-1-ol (dronabinol), eptazocine, ethoheptazine, ethyl methyl thiambutene, 4,5α-epoxy-3-ethoxy-17-methyl-7-morphinen-6α-ol (ethylmorphine), etonitazene, 4,5α-epoxy-7α-(1-hydroxy-1-methylbutyl)-6-methoxy-17-methyl-6,14-*endo*-etheno-morphinan-3-ol (etorphine), *N*-ethyl-3-phenyl-8,9,10-trinorbornan-2-ylamine (fencamfamine), 7-[2-(α-methylphenethylamino)-ethyl] theophylline (fenethylline), 3-(α-methylphenethylamino) propionitrile (fenproporex), *N*-(1-phenetyl-4-piperidyl) propionanilide (fentanyl), heroin, 4,5α-epoxy-3-methoxy-17-methyl-6-morphinanone (hydrocodone), 4,5α-epoxy-3-hydroxy-17-methyl-6-morphinanone (hydromorphone), hydroxypethidine, isomethadone, hydroxymethyl morphinan, 1-[4-(3-hydroxyphenyl)-1-methyl-4-piperidyl]-1-propanone (ketobemidone), (3*S*,6*S*)-6-dimethylamino-4,4-diphenylheptan-3-yl acetate (levacetylmethadol (LAAM)), (-)-6-dimethylamino-4,4-diphenyl-3-heptanone (levomethadone), (-)-17-methyl-3-morphinanol (levorphanol), levophenacyl morphan, lofentanil, 5-(4-chlorophenyl)-2,5-dihydro-3*H*-imidazo[2,1-*a*]isoindol-5-ol (mazindol), *N*-(3-chloropropyl)-α-methylphenetylamine (mefenorex), meperidine, meptazinol, metazocine, methylmorphine, *N*,α-dimethyl phenethylamine (methamphetamine), (±)-6-dimethylamino-4,4-diphenyl-3-heptanone (methadone), methyl-[2-phenyl-2-(2-piperidyl)acetate] (methyl phenidate), 3,3-diethyl-5-methyl-2,4-piperidinedione (methyprylone), 2-(benzhydrylsulfinyl) acetamide (modafinil), 4,5α-epoxy-17-methyl-7-morphinene-3,6α-diol (morphine), myrophine, (±)-*trans*-3-(1,1-dimethylheptyl)-7,8,10,10α-tetrahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo[*b,d*]pyran-9(α*H*)-one (nabilone), nalbuphen, narceine, nicomorphine, norlevorphanol, 6-dimethylamino-4,4-diphenyl-3-hexanone (normethadone), normorphine, norpipanone, the coagulated juice of the plants belonging to the species *Papaver somniferum* (opium), 4,5α-epoxy-14-hydroxy-3-methoxy-17-methyl-6-morphinanone (oxycodone), oxymorphone, plants and plant parts of the plants belonging to the species *Papaver somniferum* (including the subspecies *setigerum*) (*Papaver somniferum*), papaveretum, 2-imino-5-phenyl-4-oxazolidinone (pernoline), 1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol (pentazocine), ethyl-(1-methyl-4-phenyl-4-piperidine-carboxylate) (pethidine), phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, pholcodeine, 3-methyl-2-phenylmorpholine (phenmetrazine), α,α-dimethylphenethylamine (phentermine), α-(2-piperidyl)benzhydryl alcohol (pipradol), 1'-(3-cyano-3,3-diphenylpropyl)[1,4'-bipiperidine]-4'-carboxamide (piritramide), profadol, proheptazine, promedol, properidine, propoxyphene, *N*-(1-methyl-2-piperidinoethyl)-*N*-(2-pyridyl) propionamide, methyl{3-[4-methoxycarbonyl-4-(*N*-phenylpropanamido)-piperidino]propanoate} (remifentanil), *N*-(4-methoxymethyl-1-[2-(2-thienyl)ethyl]-4-piperidyl}propionanilide (sufentanil), ethyl-(2-dimethylamino-1-phenyl-3-cyclohexene-1-

carboxylate) (tilidine (*cis* and *trans*)), tramadol, (1R*,2R*)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl) phenol, (1R,2R,4S)-2-[dimethylamino)methyl-4-(*p*-fluorobenzyloxy)-1-(*m*-methoxyphenyl) cyclohexanol, each optionally in the form of corresponding stereoisomeric compounds as well as corresponding derivatives, especially esters or ethers, and all being physiologically compatible compounds, especially salts and solvates.

The compounds (1R*,2R*)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl) phenol and (1R,2R,4S)-2-(dimethylamino)methyl-4-(*p*-fluorobenzyloxy)-1-(*m*-methoxyphenyl) cyclohexanol, their physiologically compatible compounds, especially their hydrochlorides, as well as methods for preparing same are known from, e.g., EP-A 693 475 and EP-A 780 369. The corresponding specifications are hereby introduced as reference and are considered to be part of the disclosure.

The dosage form according to the present invention, containing a combination of at least two of the components a)-d), is also suitable for preventing the abuse of stimulants, preferably those that are selected from the group comprising amphetamines, norpseudoephedrine, methyl phenidate, and optionally the respective corresponding, physiologically compatible compounds thereof, especially the bases, salts and solvates thereof.

If the combination for safeguarding the dosage form according to the present invention from abuse contains the component (a), the substances suitable for use according to the present invention as substances irritating the nasal and/or pharyngeal region include all the substances that elicit a reaction of the body, which is either so unpleasant for the abuser that he does not want to or cannot continue the administration, e.g., a burning, or counteracts the absorption of the corresponding active ingredient in a physiological manner, e.g., by increased nasal secretion production or sneezing. In addition, it was found that these substances that irritate the nasal and/or pharyngeal region usually also cause a very unpleasant feeling and even unbearable pain upon parenteral, especially intravenous administration, so that the abuser does not want to or cannot continue the administration any longer.

Especially suitable substances that irritate the nasal and/or pharyngeal region are the substances that cause burning, itching, an urge to sneeze, increased production of secretion or a combination of at least two of these irritations. Corresponding substances and the quantities in which they are usually to be used are known per se to the person skilled in the art or can be determined by simple preliminary experiments.

The substance of component (a) that irritates the nasal and/or pharyngeal region is preferably based on one or more constituents of at least one pungent drug.

Corresponding pungent drugs are known per se to the person skilled in the art and are described, for example, in *Pharmazeutische Biologie - Drogen und ihre Inhaltsstoffe* [Pharmaceutical Biology - Drugs and their Constituents], 2nd, revised edition, Gustav Fischer Verlag, Stuttgart-New York, 1982, pp. 82 ff. The corresponding description is hereby introduced as reference and is considered to be part of the disclosure.

The dosage form according to the present invention may preferably contain the plant parts of the corresponding pungent drugs in an amount of 0.01 wt.% to 30 wt.% and especially preferably 0.1 wt.% to 0.5 wt.%, always relative to the total weight of the dosage unit.

If one or more constituents of corresponding pungent drugs are used, their amount in the dosage

form according to the present invention is preferably between 0.001 wt.% and 0.005 wt.% relative to the total weight of the dosage unit.

A dosage unit is defined as a separate or separable dosage unit, for example, a tablet or a capsule.

The dosage form according to the present invention preferably contains as component (a) one or more constituents of at least one pungent drug, selected from the group comprising allii sativi bulbus, asari rhizoma c. herba, calami rhizoma, capsici fructus (paprika), capsici fructus acer (cayenne pepper), curcumae longae rhizoma, curcumae xanthorrhizae rhizoma, galangae rhizoma, myristicae semen, piperis nigri fructus (pepper), sinapis albae (erucae) semen, sinapis nigri semen, zedoariae rhizoma and zingiberis rhizoma, especially preferably from the group comprising capsici fructus (paprika), capsici fructus acer (cayenne pepper) and piperis nigri fructus (pepper).

The constituents of the pungent drugs are preferably *o*-methoxy(methyl) phenol compounds, mustard oils or sulfide derivatives or compounds derived therefrom.

The constituent of the pungent drugs is selected especially preferably from the group comprising myristicin, elemicin, isoeugenol, beta-asarone, saffrole, gingerols, xanthorrhizol, capsaicinoids, preferably capsaicin, piperine, preferably *trans*-piperine, glucosinolates, preferably those based on nonvolatile mustard oils, especially preferably those based on *p*-hydroxybenzyl mustard oil, methyl mercapto mustard oil or methyl sulfonyl mustard oil, and compounds derived from these constituents.

Another possibility of additionally safeguarding the dosage form according to the present invention from abuse is to add to it at least one agent that increases the viscosity as an additional abuse-preventing component (b), which forms a gel in an extract obtained from the dosage form with the aid of a required minimum quantity of an aqueous liquid, which said gel continues to be able to be visually distinguished upon introduction into an additional quantity of an aqueous liquid.

Visual distinguishability in the sense of the present invention means that the gel containing the active ingredient, which was formed with the aid of a required minimum quantity of aqueous liquid, remains essentially insoluble and contiguous upon introduction, preferably by means of an injection needle, into an additional amount of an aqueous liquid having a temperature of 37°C and cannot be dispersed in a simple manner such that a safe parenteral, especially intravenous administration would be possible. The duration of the visual distinguishability is preferably at least one minute.

The increase in the viscosity of the extract causes that the flow of the extract through a needle or the injectability of the extract becomes more difficult or even impossible. Furthermore, it causes that upon introduction into an additional quantity of aqueous liquid, e.g., by injection into blood, the extract obtained will initially be preserved in the form of an extensively contiguous thread, which can be divided into smaller fragments by mechanical action, but it cannot be dispersed or even dissolved such as to make possible a parenteral, especially intravenous administration without risks. Combined with component (a) and/or (d), this additionally leads to an unpleasant burning and/or vomiting.

The intravenous administration of a corresponding extract would therefore lead with a high probability to the clogging of vessels, associated with severe emboli and even death of the abuser.

To check whether a viscosity-increasing agent is suitable for use as component (b) in the dosage form according to the present invention, the agent is formulated in a corresponding dosage form, the dosage form thus obtained is comminuted, preferably in a mortar, and extracted with 10 m*L* of water at a temperature of 25°C. If a gel is formed in the process, which meets the above-described conditions, the corresponding viscosity-increasing agent is suitable for preparing the dosage form according to the present invention.

If safeguarding from abuse is provided for in the dosage form according to the present invention by means of a combination containing component (b), one or more viscosity-increasing agents are preferably used, which are selected from the group comprising microcrystalline cellulose containing 11 wt.% of carboxymethyl cellulose sodium (Avicel® RC 591), carboxymethyl cellulose sodium (Blanose®, CMC-Na C300P®, Frimulsion BLC-5®, Tylose C300 P®), polyacrylic acid (Carbopol® 980 NF, Carbopol® 981), carob bean powder (Cesagum® LA-200, Cesagum® LID/150, Cesagum® LN-1), citrus pectin (Cesapectin® HM Medium Rapid Set), waxy corn starch (C*Gel 04201®), sodium alginate (Frimulsion ALG (E401)®), guar gum powder (Frimulsion BM®, Polygum 26/1-75®), iota-carragheen (Frimulsion D021®), karaya gum, gellan gum (Kelcogel F®, Kelcogel LT100®), galactomannan (Meyprogat 150®), tara powder (Polygum 43/1®), propylene glycol alginate (Protanal-Ester SD-LB®), apple pectin, pectin from lemon peel, sodium hyaluronate, tragacanth, tara gum (Vidogum SP 200®), fermented polysaccharide-Welan Gum (K1A96), and xanthan gum (Xantural 180®). The names given in parentheses are the trade names under which the respective materials are available on the market. In general, an amount of 0.1 wt.% to 5 wt.% of the said viscosity-increasing agent(s) is sufficient to meet the above-described conditions.

The viscosity-increasing agents of component (b), if provided, are preferably present in the active ingredient according to the present invention in amounts of $\geq$ 5 mg per dosage form, i.e., per dosage unit.

In an especially preferred embodiment of the present invention, the viscosity-increasing agents used as component (b) in the combination safeguarding from abuse are those which form a gel enclosing air bubbles during extraction from the dosage form with the required minimum quantity of aqueous liquid. The gels thus obtained are characterized by a turbid appearance, by which the potential abuser is additionally warned optically and is prevented from administering same parenterally.

It is surprisingly possible to combine the active ingredients and at least the viscosity-increasing agent in the dosage form according to the present invention without separating them from one another in space, without the release of the active ingredient being compromised during the administration of the dosage form as intended compared with a corresponding dosage form that does not contain the viscosity-increasing agent.

However, it is, of course, also possible to combine the viscosity-increasing agent and the active ingredients in the dosage form in an arrangement in which they are separated from one another in space, as will be described below.

Furthermore, the dosage form according to the present invention may contain in the combination

for safeguarding from abuse the component (c), namely, one or more antagonists for the active ingredient or the active ingredients that could be potentially subject to abuse, wherein the amount of the antagonist should preferably be present in such a way that it is separated in space from the active ingredient and component (a) and/or (b) and should not exert any action during use as intended.

Suitable antagonists for preventing the abuse of the active ingredients are known per se to the person skilled in the art and may be present in the dosage form according to the present invention as such or in the form of corresponding derivatives, especially esters or ethers, or in the form of corresponding, physiologically compatible compounds, especially in the form of their salts or solvates.

If the active ingredient present in the dosage form is an opiate or an opioid, an antagonist selected from the group comprising naloxone, naltrexone, nalmefene, nalid, nalmexone, nalorphine or naluphine is preferably used as the antagonist, each optionally in the form of a corresponding, physiologically compatible compound, especially in the form of a base, a salt or solvate. If provisions are made for the use of component (c), the corresponding antagonists are preferably used in an amount of $\geq$ 10 mg, especially preferably in an amount of 10 mg to 100 mg and particularly preferably in an amount of 10 mg to 50 mg per dosage form, i.e., per dosage unit.

If the dosage form according to the present invention contains as the active ingredient a stimulant, the antagonist is preferably a neuroleptic, preferably one selected from the group comprising haloperidol, promethazine, fluophenozine, perphenazine, levomepromazine, thioridazine, perazine, chlorpromazine, chlorprotheaxin [sic - chlorprothixene? - Tr.Ed.], zuclopantexol, flupentexol, prithipendyl, zotepine, penperidol, piparmerone, melperol, and bromperidol.

The dosage form according to the present invention preferably contains these antagonists in a usual therapeutic dosage known to the person skilled in the art, especially preferably in a quantity that is two to three times the usual dosage per dosage unit.

If the combination for safeguarding the dosage form according to the present invention from abuse contains the component (d), it may contain at least one emetic, which should be preferably present in such an application [sic - probably typo in German original for word meaning "arrangement" - Tr.Ed.] that it is separated in space from the component (a) and/or (b) that may optionally be present and the active ingredient and exert no action in the body in case of use as intended.

Suitable emetics for preventing the abuse of the active ingredients are known per se to the person skilled in the art and may be present in the dosage form according to the present invention as such or in the form of corresponding derivatives, especially esters or ethers, or in the form of corresponding, physiologically compatible compounds, especially in the form of their salts or solvates.

If the combination for safeguarding from abuse contains component (d), an emetic based on one or more constituents of radix ipecacuanhae (ipecac), preferably based on the constituent emetine, is preferably considered for use in the dosage form according to the present invention, as is described, e.g., in *Pharmazeutische Biologie - Drogen und ihre Inhaltsstoffe* [Pharmaceutical Biology - Drugs and their Constituents] by Dr. Hildebert Wagner, 2nd, revised edition, Gustav Fischer Verlag, Stuttgart-New York, 1982. The corresponding description in the literature is

hereby introduced as reference and is considered to be part of the disclosure.

The dosage form according to the present invention may preferably contain as component (d) the emetic emetine, preferably in an amount of $\geq$ 10 mg, especially preferably $\geq$ 20 mg and particularly preferably in an amount of $\geq$ 40 mg per dosage form, i.e., dosage unit.

Apomorphine may likewise be preferably used as an emetic in the combination for safeguarding from abuse according to the present invention, preferably in an amount of $\geq$ 3 mg, especially preferably $\geq$ 5 mg and especially preferably $\geq$ 7 mg per dosage unit.

The dosage form according to the present invention may be formulated in many different ways according to usual methods known to the person skilled in the art. Methods for formulating the dosage form are known to the person skilled in the art, for example, from *Coated Pharmaceutical Dosage Forms - Fundamentals, Manufacturing Techniques, Biopharmaceutical Aspects, Test Methods and Raw Materials* by Kurt H. Bauer, K. Lehmann, Hermann P. Osterwald, Rothgang Gerhart, 1st edition, 1998, Medpharm Scientific Publishers. The corresponding description is hereby introduced as reference and is considered to be part of the disclosure.

The dosage forms according to the present invention are preferably suitable for oral administration.

In a preferred embodiment, the dosage form according to the present invention is in the form of a tablet, a capsule or in the form of an oral osmotic therapeutic system (OROS).

According to an especially simple way of formulating the dosage form according to the present invention, two or more of the components (a)-(d) are mixed with the active ingredient or the active ingredients and optionally physiologically compatible inactive ingredients, and this mixture is filled into a capsule or made into a tablet, if the tolerance limits are respected with respect to the components (c) and (d) during the oral use as intended. It shall be borne in mind with this way of formulating the dosage form that the components (c) and/or (d) be formulated or used in such a low dose that they cannot exert any action compromising the patient or the efficacy of the active ingredient in case of administration of the dosage form as intended.

In another preferred embodiment, the dosage form according to the present invention contains the component (d) in a dose that is selected to be such that no adverse effect is caused in case of oral use as intended. However, nausea is induced if the intended dosage of the dosage form is accidentally exceeded, especially by children or in case of abuse. The corresponding quantity of component (d), which is still tolerated by the patient in case of oral use as intended, can be determined by the person skilled in the art by simple preliminary experiments.

Oral osmotic therapeutic systems as well as suitable materials and methods for manufacturing same are known per se to the person skilled in the art, for example, from US 4,612,008, US 4,765,989 and US 4,783,337. The corresponding specifications are hereby introduced as reference and are considered to be part of the disclosure.

However, if a combination for safeguarding the dosage form, which contains the components (c) and/or (d), is provided, these components should be preferably used at such a high dosage that

they produce an intense adverse effect in the abuser during the abusive use of the dosage form. This can preferably be achieved by the separation in space of at least the active ingredient or active ingredients from the components (c) and/or (d), the active ingredient or the active ingredients being preferably present in at least one subunit (A) and the components (c) and/or (d) being present in at least one subunit (B), and the components (c) and (d) not exerting their action in the body in case of use of the dosage form as intended.

If the dosage form according to the present invention contains both the components (c) and (d), these may be present in the same subunit (B) or in different subunits (B). If present, both components (c) and (d) are preferably present in one and the same subunit (B).

Subunits in the sense of the present invention are solid formulations that contain, besides the usual inactive ingredients known to the person skilled in the art, only the active ingredient(s) and optionally at least one of the components (a) and/or (b) that may optionally be present or only the antagonist(s) and/or the emetic (the emetics) and optionally at least one of the components (a) and/or (b) that may be optionally present.

An essential advantage of the separate formulation of the active ingredients from the components (c) and (d) in subunits (A) and (B) of the dosage form according to the present invention is that in case of use as intended, the components (c) and/or (d) are not practically released in the body or are released in such small quantities only that they do not exert any action compromising the patient or the therapeutic result or are released during their passage through the patient's body only at such release sites at which resorption sufficient for their efficacy does not take place. The components (c) and/or (d) are practically not released in the patient's body in case of administration of the dosage form as intended. The person skilled in the art understands that these above-mentioned conditions may vary depending on the particular components (c) and (d) used as well as the formulation of the subunits and of the dosage form. The formulation that is optimal for the particular dosage form can be determined by simple preliminary experiments.

If a corresponding dosage form according to the present invention, which contains the components (c) and/or (d) in subunits (B), is manipulated for the purpose of the abusive administration of the active ingredient, e.g., by crushing in a mortar or optionally extraction of the powder thus obtained with a suitable extractant, the particular component (c) and/or (d) is also contained, besides the active ingredient and optionally (a) and/or (b) in such form in which it cannot be separated from the active ingredient in a simple manner, so that it exerts its action in the body upon the administration of the manipulated dosage form, especially in case of oral and/or parenteral administration, and one of the components (c) and/or (d) may possibly additionally produce a corresponding adverse effect in the abuser and thus prevent the abuse of the dosage form.

A dosage form according to the present invention, in which the active ingredient or the active ingredients is/are separated in space from the components (c) and (d), preferably by formulation in different subunits, can be formulated in many different ways, and the corresponding subunits may be present in the dosage form according to the present invention in any desired arrangement in space in relation to one another if the above-mentioned conditions for the release of the components (c) and/or (d) are met.

The person skilled in the art understands that the components (a) and/or (b) that may be present may be preferably formulated in the dosage form according to the present invention both in the

respective subunits (A) and (B) and in the form of independent subunits corresponding to the subunits (A) and (B) as long as the safeguarding of the dosage form from abuse and the release of the active ingredient in case of use as intended are not compromised by the manner of formulation.

In a preferred embodiment of the dosage form according to the present invention, the subunits (A) and (B) are in the multiparticulate form, microtablets, microcapsules, micropellets, granules, spheroids, beads or pellets being preferred, and the same form, i.e., shape, being selected for both the subunit (A) and subunit (B), so that separation of the subunits (A) and (B) by mechanical selection is not possible. The multiparticulate forms preferably have a size in the range of 0.1 mm to 3 mm and preferaBly from 0.5 mm to 2 mm.

The subunits (A) and (B) in the multiparticulate form may also be preferably filled into a capsule, suspended in a liquid or a gel or made into a tablet, the respective final formulations being performed such that the subunits (A) and (B) are also preserved in the resulting dosage form.

The respective multiparticulate subunits (A) and (B) of identical shape should also not be able to be visually distinguished from one another, so that they cannot be separated from one another by the abuser by a simple sorting. This can be guaranteed, for example, by the application of identical coatings, which can also assume other functions, e.g., the retarding of one or more active ingredients or an enteric coating of the particular subunits, besides this equalizing function.

In another preferred embodiment of the present invention, the subunits (A) and (B) are arranged in the form of layers in relation to one another.

The layered subunits (A) and (B) are preferably arranged for this purpose vertically or horizontally in relation to one another in the dosage form according to the present invention, and one or more layered subunits (A) and one or more layered subunits (B) may also be present in the dosage form, so that any other series of layers may be considered besides the preferred series of layers (A)-(B) or (A)-(B)-(A), optionally combined with layers containing the components (a) and/or (b).

Equally preferred is a dosage form according to the present invention in which the subunit (B) forms a core, which is completely enveloped by the subunit (A), and an optionally swellable separating layer (C) may be present between these layers. A corresponding structure is also preferably suitable for the above-mentioned multiparticulate forms, in which case both subunits (A) and (B) as well as a separating layer (C) that may be optionally present are formulated in the same multiparticulate form.

In another preferred embodiment of the dosage form according to the present invention, the subunit (A) forms a core, which is enveloped by the subunit (B), the latter having a channel, which leads from the core to the surface of the dosage form.

Between a layer of subunit (A) and a layer of subunit (B), the dosage form according to the present invention may have one or more, preferably one, optionally swellable separating layer (C) for separating the subunits (A) and (B) in space.

If the dosage form according to the present invention contains the layered subunits (A) and (B) as well as the separating layer (C) that may be optionally present in an at least partially vertical or

horizontal arrangement, it is preferably in the form of a tablet, a coextrudate or a laminate.

In an especially preferred embodiment, the free surface of subunit (B) may be completely enveloped with at least one barrier layer (D) preventing the release of the components (c) or (d) and optionally at least part of the free surface of the subunit(s) (A) and optionally at least part of the free surface of the separating layer(s) (C) that may be optionally present may be coated with such a barrier layer.

Particularly preferred is also an embodiment of the dosage form according to the present invention that has a vertical or horizontal arrangement of the layers of the subunits (A) and (B) and at least one push layer (P) arranged between them as well as optionally a separating layer (C), in which all free surfaces of the layer structure comprising the subunits (A) and (B), the push layer and the separating layer (C) that may be optionally present are provided with a semipermeable coating (E), which is permeable to the releasing medium, i.e., usually a physiological liquid, and essentially impermeable to the active ingredient and the components (c) and/or (d), and wherein this coating (E) has at least one opening for releasing the active ingredient in the area of the subunit (A).

A corresponding dosage form is known to the person skilled in the art, for example, under the name oral osmotic therapeutic system (OROS), and suitable materials and methods for manufacturing same are known, among other things, from US 4,612,008, US 4,765,989 and US 4,783,337. The corresponding specifications are hereby introduced as reference and are considered to be part of the disclosure.

In another preferred embodiment, subunit (A) of the dosage form according to the present invention is in the form of a tablet, whose web and optionally one of the two bases are covered with a barrier layer (B) containing the component (c) and/or (d).

The person skilled in the art understands that the inactive ingredients of the subunit(s) (A) and (B) and optionally of the separating layer(s) (C) present and/or of the barrier layer(s) (D), which said inactive ingredients are used in formulating the dosage form according to the present invention, are subject to variations depending on the arrangement of the said subunits and layers in the dosage form according to the present invention, the route of administration as well as depending on the particular active ingredient of the components (a) and/or (b) that may be optionally present and of the component (c) and/or (d). The materials, which possess the particular required properties, are known per se to the person skilled in the art.

If the release of the component (c) and/or (d) from subunit (B) of the dosage form according to the present invention is prevented by means of a coating, preferably a barrier layer, the subunit may consist of usual materials known to the person skilled in the art.

If a corresponding barrier layer (D) for preventing the release of component (c) and/or (d) is not provided, the materials of the subunits are to be selected such that release of the respective component (c) and/or (d) from the subunit (B) is practically ruled out. The materials listed below may be preferably used for this purpose, which are also suitable for forming the barrier layer.

Preferred materials are those that are selected from the group comprising alkyl celluloses, hydroxyalkyl celluloses, glucans, scleroglucans, mannans, xanthans, copolymers of poly[bis(*p*-carboxyphenoxy)-propane and sebacic acid, preferably at a molar ratio of 20:80 (available

commercially under the name Polifeprosan 20®), carboxymethyl celluloses, cellulose ethers, cellulose esters, nitrocelluloses, polymers based on (meth)acrylic acid as well as its esters, polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides,

polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, halogenated polyvinyls, polyglycolides, polysiloxanes as well as polyurethanes and their copolymers.

Especially suitable materials may be selected from the group comprising methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate (of low, medium or high molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethyl cellulose, cellulose triacetate, sodium cellulose sulfate, polymethyl methacrylate, polyethyl methacrylate, polybutyl methacrylate, polyisobutyl methacrylate, polyhexyl methacrylate, polyisodecyl methacrylate, polylauryl methacrylate, polyphenyl methacrylate, polymethyl acrylate, polyisopropyl acrylate, polyisobutyl acrylate, polyoctadecyl acrylate, polyethylene, low-density polyethylene, high-density polyethylene, polypropylene, polyethylene glycol, polyethylene oxide, polyethylene terephthalate, polyvinyl alcohol, polyvinyl isobutyl ether, polyvinyl acetate, and polyvinyl chloride.

Especially suitable copolymers may be selected from the group comprising copolymers of butyl methacrylate and isobutyl methacrylate, copolymers of methyl vinyl ether and maleic acid with increased molecular weight, copolymers of methyl vinyl ether and maleic acid monoethyl ester, copolymers of methyl vinyl ether and maleic anhydride as well as copolymers of vinyl alcohol and vinyl acetate.

Other materials that are especially suitable for formulating the barrier layer are starch-filled polycaprolactone (WO98/20073), aliphatic polyester amides (DE 19 753 534 A1, DE 19 800 698 A1, EP 0 820 698 A1), aliphatic and aromatic polyester urethanes (DE 19 822 979), polyhydroxyalkanoates, especially polyhydroxybutyrates, polyhydroxyvalerates, casein (DE 4 309 528), polylactides and copolylactides (EP 0 980 894 A1). The corresponding specifications are hereby introduced as reference and are considered to be part of the disclosure.

The above-mentioned materials may be optionally mixed with other usual inactive ingredients known to the person skilled in the art, preferably those selected from the group comprising glyceryl monostearate, semisynthetic triglyceride derivatives, semisynthetic glycerides, hydrogenated castor oil, glyceryl palmitostearate, glyceryl behenate, polyvinyl pyrrolidone, gelatin, magnesium stearate, stearic acid, sodium stearate, talc, sodium benzoate, boric acid and colloidal silica, fatty acids, substituted triglycerides, glycerides, polyoxyalkylene glycols and their derivatives.

If the dosage form according to the present invention has a separating layer (D), this layer, as well as the uncoated subunit (B), may preferably consist of the above materials described for the barrier layer. The person skilled in the art understands that the release of the active ingredient or of component (c) and/or (d) from the particular subunit can also be controlled by varying the thickness of the separating layer.

The dosage form according to the present invention may contain one or more active ingredients at least in the sustained-release form, the retarding being able to be achieved by means of usual materials and methods known to the person skilled in the art, for example, by embedding the

active ingredient in a retarding matrix or by applying one or more retarding coatings. However, the release of the active ingredient must be controlled such that the above-mentioned conditions will always be met, e.g., that the active ingredient or the active ingredients is/are released

practically completely in case of the use of the dosage form as intended before the component (c) and/or (d) could exert an adverse effect.

If the dosage form according to the present invention is intended for oral administration, it may preferably also have an enteric coating, which dissolves as a function of the pH value of the releasing environment. It can be achieved due to this coating that the dosage form according to the present invention will pass through the stomach without dissolving and the active ingredient is released in the intestinal tract only. The enteric coating preferably dissolves at a pH value between 5 and 7.5.

Corresponding materials and methods for retarding active ingredients as well as for applying the enteric coatings are known to the person skilled in the art from, e.g., *Coated Pharmaceutical Dosage Forms - Fundamentals, Manufacturing Techniques, Biopharmaceutical Aspects, Test Methods and Raw Materials* by Kurt H. Bauer, K. Lehmann, Hermann P. Osterwald, Rothgang, Gerhart, 1st edition, 1998, Medpharm Scientific Publishers. The corresponding description in the literature is hereby introduced as reference and is considered to be part of the disclosure.

The dosage forms according to the present invention have the advantage that they are safeguarded from any kind of abuse, preferably from oral, nasal and parenteral abuse, by any desired combination of two or more of the components (a)-(d), without the patient being treated being compromised or without a reduction of the efficacy of the particular active ingredient having to be feared in case of use as intended. They can be manufactured in a simple manner and at a comparatively low cost.

The present invention will be explained below on the basis of examples. These explanations are only exemplary and do not limit the general inventive idea.

Examples:

Example 1

Matrix tablets having the following composition per tablet

(-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl) phenol hydrochloride	100 mg
Hydroxypropyl methyl cellulose (Metolose 90 SH 100.000 from Shinetsu), 100,000 mPa·s	70 mg
Xanthan, NF	10 mg
Microcrystalline cellulose (Avicel PH 102 from FMC)	113 mg
Cayenne pepper	10 mg
Highly disperse silica	4 mg
Magnesium stearate	3 mg
Total amount	310 mg

were prepared in the following manner in a batch of 1,000 tablets: All components were weighed and screened on a Quadro Comil U10 screening machine using a screen size of 0.813 mm, mixed in a container mixer (Bohle LM 40) for 15 minutes ± 15 sec at a speed of 20 ± 1 rpm and pressed into arched tablets with a diameter of 10 mm, an arch radius of 8 mm and a mean tablet weight of 310 mg on a Korsch EK0 eccentric press.

One of the tablets is crushed in a mortar and shaken with 10 m*L* of water. A viscous, turbid suspension is formed. After settling of the coarse, solid components of the suspension, the suspension is drawn up into a syringe with a 0.9-mm needle, but the drawing up is made difficult by the viscosity. The extraction liquid drawn up is injected into water having a temperature of 37°C, and threads having the diameter of the needle are clearly extruded, which are immiscible with the water. While stirring, the threads are divided but not dissolved; the fragments of the threads are still recognizable to the naked eye after a few minutes. Clogs would develop in the vessels upon the injection of such an extract into blood vessels.

A tablet crushed in a mortar was drawn out into a line with a length of 10 cm and drawn into the nose through a tube. The nose was irritated to the extent already after the first cm that the urgent need to remove the powder was generated by sneezing, and it was no longer possible to introduce any more of the remaining powder through the nose. The nasal irritation subsided after the sneezing and the irritation disappeared completely after about 10 minutes. A need to repeat the procedure fails to develop.

Example 2

Matrix tablets having the following composition per tablet

(-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl) phenol hydrochloride	100 mg
Hydroxypropyl methyl cellulose (Metolose 90 SH 100.000, Shinetsu), 100,000 mPa·s	40 mg
Xanthan, NF	40 mg
Microcrystalline cellulose (Avicel PH 102, FMC)	113 mg
Cayenne pepper	10 mg
Highly disperse silica	4 mg
Magnesium stearate	3 mg
Total amount	310 mg

were prepared as described in Example 1.

One of the tablets was crushed in a mortar and shaken with 10 m*L* of water. A viscous, turbid suspension was formed, whose viscosity was higher than in Example 1; the number of enclosed air bubbles was increased as well. After settling the coarse, solid components of the suspension, the suspension is drawn up into a syringe with a 0.9-mm needle, and drawing up is made very difficult by the viscosity. The extraction liquid drawn up is injected into water having a temperature of 37°C, while threads with the diameter of the needle, which are immiscible with the water, are clearly extruded. The threads are divided while stirring, but not dissolved; fragments of the threads are still recognizable to the naked eye after a few minutes. Clogs would develop in the vessels upon the injection of such an extract into blood vessels.

A tablet crushed in a mortar was drawn out into a line with a length of 10 cm and drawn into the nose through a tube. The nose was irritated to the extent already after the first cm that the urgent need to remove the powder was generated by sneezing, and it was no longer possible to introduce any more of the remaining powder through the nose. The nasal irritation subsided after the sneezing and the irritation disappeared completely after about 10 minutes. A need to repeat the procedure fails to develop.

Example 3

Matrix tablets having the following composition per tablet

(-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl) phenol hydrochloride	100 mg
Xanthan, NF	80 mg
Microcrystalline cellulose (Avicel PH 102, FMC)	113 mg
Cayenne pepper	10 mg
Highly disperse silica	4 mg
Magnesium stearate	3 mg
Total amount	310 mg

were prepared as described in Example 1.

One of the tablets was crushed in a mortar and shaken with 10 m*L* of water. A viscous, turbid suspension was formed, whose viscosity was higher than in Example 1; the number of enclosed air bubbles was increased as well. After settling the coarse, solid components of the suspension, the suspension is drawn up into a syringe with a 0.9-mm needle, and drawing up is made very difficult by the viscosity. The extraction liquid drawn up is injected into water having a temperature of 37°C, while threads with the diameter of the needle, which are immiscible with the water, are clearly extruded. The threads are divided while stirring, but not dissolved; fragments of the threads are still recognizable to the naked eye after a few minutes. Clogs would develop in the vessels upon the injection of such an extract into blood vessels.

A tablet crushed in a mortar was drawn out into a line with a length of 10 cm and drawn into the nose through a tube. The nose was irritated to the extent already after the first cm that the urgent need to remove the powder was generated by sneezing, and it was no longer possible to introduce any more of the remaining powder through the nose. The nasal irritation subsided after the sneezing and the irritation disappeared completely after about 10 minutes. A need to repeat the procedure fails to develop.

Examples 4-7

Matrix tablets having the following composition per tablet

Example	4	5	6	7
(-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl) phenol hydrochloride	100 mg	100 mg	100 mg	100 mg
Hydroxypropyl methyl cellulose (Metolose 90 SH 100.000, Shinetsu), 100,000 mPa·s	80 mg	80 mg	80 mg	80 mg
Carboxymethyl cellulose (Tylose C300)	10 mg			
Carboxymethyl cellulose (Tylose C600)		10 mg		
Hydroxyethyl cellulose (Tylose H300)			10 mg	
Hydroxyethyl cellulose (Tylose H4000)				10 mg
Microcrystalline cellulose (Avicel PH 102, FMC)	113 mg	113 mg	113 mg	113 mg
Cayenne pepper	10 mg	10 mg	10 mg	10 mg
Highly disperse silica	4 mg	4 mg	4 mg	4 mg
Magnesium stearate	3 mg	3 mg	3 mg	3 mg
Total amount	320 mg	320 mg	320 mg	320 mg

were prepared as described in Example 1.

The tablets were crushed in a mortar and shaken with 10 m*L* of water. A viscous, turbid suspension was formed; air bubbles were enclosed as well. After settling the coarse, solid components of the suspension, the suspension is drawn up into a syringe with a 0.9-mm needle, and drawing up is made very difficult by the viscosity. The extraction liquid drawn up is injected into water having a temperature of 37°C, while threads with the diameter of the needle, which are immiscible with the water, are clearly extruded. The threads are divided while stirring, but not dissolved; fragments of the threads are still recognizable to the naked eye after a few minutes. Clogs would develop in the vessels upon the injection of such an extract into blood vessels.

A tablet crushed in a mortar was drawn out into a line with a length of 10 cm and drawn into the nose through a tube. The nose was irritated to the extent already after the first cm that the urgent need to remove the powder was generated by sneezing, and it was no longer possible to introduce any more of the remaining powder through the nose. The nasal irritation subsided after the sneezing and the irritation disappeared completely after about 10 minutes. A need to repeat the procedure fails to develop.

Examples 8-13

Matrix tablets having the following composition per tablet

Example	8	9	10	11	12	13
Morphine sulfate pentahydrate	60 mg	60 mg	60 mg	60 mg	60 mg	60 mg
Hydroxy-propyl methyl cellulose (Metolose 90 SH 15.000, Shinetsu), 15,000 mPa·s	60 mg	60 mg	60 mg	60 mg	60 mg	60 mg
Xanthan, NF	10 mg	30 mg				
Carboxy-methyl cellulose (Tylose C300)			10 mg			
Carboxy-methyl cellulose (Tylose C600)				10 mg		
Hydroxyethyl cellulose (Tylose H300)					10 mg	
Hydroxyethyl cellulose (Tylose H4000)						10 mg
Microcrystalline cellulose (Avicel PH, FMC)	112.9 mg	112.9 mg	112.9 mg	112.95 mg	112.95 mg	112.95 mg
Capsaicin, micronized	0.1 mg	0.1 mg	0.1 mg	0.05 mg	0.05 mg	0.05 mg
Highly disperse silica	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg
Magnesium stearate	3 mg	3 mg	3 mg	3 mg	3 mg	3 mg

were prepared as described in Example 1.

One tablet was crushed in a mortar and shaken with 10 m*L* of water. A viscous, turbid suspension was formed; air bubbles were enclosed as well. After settling the coarse, solid components of the suspension, the suspension is drawn up into a syringe with a 0.9-mm needle, and drawing up is made very difficult by the viscosity. The extraction liquid drawn up is injected into water having a temperature of 37°C, while threads with the diameter of the needle, which are immiscible with the water, are clearly extruded. The threads are divided while stirring, but not

dissolved; fragments of the threads are still recognizable to the naked eye after a few minutes. Clogs would develop in the vessels upon the injection of such an extract into blood vessels.

A tablet crushed in a mortar was drawn out into a line with a length of 10 cm and drawn into the nose through a tube. The nose was irritated to the extent already after the first cm that the urgent need to remove the powder was generated by sneezing, and it was no longer possible to introduce any more of the remaining powder through the nose. The nasal irritation subsided after the sneezing and the irritation disappeared completely after about 10 minutes. A need to repeat the procedure fails to develop.

Examples 14-18

Capsules having the following composition of the simple powder mixture per capsule (capsule size 4)

Example	14	15	16	17	18
Morphine sulfate pentahydrate	20 mg	20 mg	20 mg	20 mg	20 mg
Xanthan, NF	10 mg				
Carboxymethyl cellulose (Tylose C300)		10 mg			
Carboxymethyl cellulose (Tylose C600)			10 mg		
Hydroxyethyl cellulose (Tylose H300)				10 mg	
Hydroxyethyl cellulose (Tylose H4000)					10 mg
Microcrystalline cellulose (Avicel PH 102, FMC)	63 mg	63 mg	63 mg	63 mg	63 mg
Cayenne pepper	5 mg	5 mg	5 mg	5 mg	5 mg
Highly disperse silica	1 mg	1 mg	1 mg	1 mg	1 mg
Magnesium stearate	1 mg	1 mg	1 mg	1 mg	1 mg

The powder from the capsules was crushed in a mortar and shaken with 10 m*L* of water. A viscous, turbid suspension was formed; air bubbles were enclosed as well. After settling the coarse, solid components of the suspension, the suspension is drawn up into a syringe with a 0.9-mm needle, and drawing up is made very difficult by the viscosity. The extraction liquid drawn up is injected into water having a temperature of 37°C, while threads with the diameter of the needle, which are immiscible with the water, are clearly extruded. The threads are divided while stirring, but not dissolved; fragments of the threads are still recognizable to the naked eye after a few minutes. Clogs would develop in the vessels upon the injection of such an extract into blood vessels.

A tablet crushed in a mortar was drawn out into a line with a length of 10 cm and drawn into the nose through a tube. The nose was irritated to the extent already after the first cm that the urgent need to remove the powder was generated by sneezing, and it was no longer possible to introduce any more of the remaining powder through the nose. The nasal irritation subsided after the

sneezing and the irritation disappeared completely after about 10 minutes. A need to repeat the procedure fails to develop.

The following quantity data are always related to the composition of a dosage form. One batch of a manufacturing run consists of 1,000 such dosage forms.

Example 19

Dry coated tablets

Core

Emetine	50 mg
Hydrogenated castor oil (Cutina HR)	50 mg

Emetine and finely powdered hydrogenated castor oil are mixed and pressed into round, biconvex tablets with a diameter of 6.5 mm on a tabletting press.

Dry coating

Morphine sulfate pentahydrate	60 mg
Methyl hydroxypropyl cellulose 100 000 m·Pas (Metolose 90 SH 100,000, Shinetsu)	100 mg
Microcrystalline cellulose (Avicel PH 102)	155 mg
Lactose monohydrate	165 mg
Cayenne pepper	10 mg
Magnesium stearate	5 mg
Colloidal silica	5 mg

All dry coating components were mixed, about 250 mg of the mixture were filled into the tablet die in a tabletting press with a mold for 13 mm biconvex tablets, the 6.5-mm core was inserted in a centered manner, the remaining 250 mg of the dry coating mixture were filled in, and the dry coating was pressed around the core.

Example 20

Dry coated tablets

Core

Emetine	50 mg
Hydrogenated castor oil (Cutina HR)	50 mg

Emetine and finely powdered hydrogenated castor oil are mixed and pressed into round, biconvex tablets with a diameter of 6.5 mm on a tabletting press.

Dry coating

Oxycodone hydrochloride	30 mg
Spray-dried lactose	290 mg
Eudragit RSPM	70 mg
Stearyl alcohol	115 mg
Cayenne pepper	10 mg
Magnesium stearate	5 mg
Talc	10 mg

Oxycodone hydrochloride, spray-dried lactose and Eudragit RSPM are mixed intimately with one another for about 5 minutes in a suitable mixer. The mixture is granulated during mixing with such an amount of purified water that a moist granulated mass is formed. The granules thus obtained are dried in a fluidized bed at 60°C and screened through a 2.5-mm screen. The granules are then dried again as described above and screened through a 1.5-mm screen. The stearyl alcohol is melted at 60-70°C and added to the granules in a mixer. After cooling, the mass is screened together with cayenne pepper, magnesium stearate and talc through a 1.5-mm screen. About 265 mg of the mixture of the granular product thus obtained are filled into the tablet die in a tabletting press with a mold for 13-mm biconvex tablets, the 6.5-mm core is inserted in a centered manner, the remaining 265 mg of the dry coating mixture are filled in, and the dry coating is pressed around the core.

Example 21

Dry coated tablets

Core

Natrexone hydrochloride	50 mg
Spray-dried lactose	46 mg
Magnesium stearate	2 mg
Colloidal silica	2 mg

All components are mixed and pressed into round, biconvex tablets with a diameter of 6,5 mm on a tabletting press.

Coating on core

Cellulose acetate containing 39.8% of acetate	9.5 mg
Macrogol 3350	0.5 mg

The coating components are dissolved in an acetone-water mixture (95:5 parts by weight) and sprayed on the cores.

Dry coating

Morphine sulfate pentahydrate	60 mg
Methyl hydroxypropyl cellulose 100 000 Mpas (Metolose 90 SH 100 000, Shinetsu)	100 mg
Microcrystalline cellulose (Avicel PH 102)	165 mg
Lactose monohydrate	155 mg
Cayenne pepper	10 mg
Magnesium stearate	5 mg
Colloidal silica	5 mg

All dry coating components are mixed, about 250 mg of the mixture are filled into the tablet die in a tabletting press with a mold for 13 mm biconvex tablets, the core coated with cellulose acetate is inserted in a centered manner, the remaining 250 mg of the dry coating mixture are filled in, and the dry coating is pressed around the core.

Example 22

Multiparticulate Form

Emetic Pellets

Emetine	50 mg
Lactose	15 mg
Microcrystalline cellulose PH101	30 mg
Hydroxypropyl cellulose with low degree of substitution (LH31, Shin-Etsu)	5 mg

All components are mixed intimately with one another in a suitable mixer for about 5 minutes. The mixture is granulated during mixing with such an amount of purified water that a moist granulated mass is formed. The granules thus obtained are extruded in a Nica extruder through a die with 1-mm extrusion openings, rounded on a Spheronizer for 5 minutes, dried in a fluidized bed at 60°C, and screened by means of a 1.5-mm screen and a 0.5-mm screen.

Coating on Emetic Pellets

Cellulose acetate containing 39.8% of acetate	9.5 mg
Macrogol 3350	0.5 mg
Titanium dioxide	0.5 mg

Quantity data per 100 mg of emetic pellets

Cellulose acetate and Macrogol are dissolved in an acetone-water mixture (95:5 parts by weight) to form a 3.8% solution, titanium dioxide is dispersed in the mixture, and the cores are sprayed with the suspension in a fluidized bed unit until the mass of the coated pellets reaches 110% of the weight of the uncoated pellets used.

Analgesic Pellets

0.5-mm nonpareils (sucrose-corn starch starter pellets, Werner)	50 mg
Morphine sulfate pentahydrate	60 mg
Povidone K 30	30 mg
Capsaicin	0.1 mg
Talc	9.9 mg

Morphine sulfate and Povidone are dissolved in purified water and talc is suspended in the solution. Capsaicin is dissolved in ethyl alcohol as a 10% solution, and the solution is added to the suspension. The suspension is sprayed at 60°C on the nonpareils and dried. The pellets are screened by means of a 1.5-mm screen and a 0.5-mm screen.

Coating on Analgesic Tablets

Ethyl cellulose dispersion (Aquacoat ECD 30, FMC Corporation)	10.0 mg
Glycerol monostearate	2.0 mg
Talc	2.0 mg
Titanium dioxide	1.0 mg

Quantity data per 150 mg of analgesic pellets; the weight of ethyl cellulose is stated as the dry weight from the 30% dispersion of the commercial product.

Ethyl cellulose dispersion is mixed with purified water at a ratio of 1:0.5 and glycerol monostearate is incorporated while stirring for at least two hours. Talc and titanium dioxide are dispersed in 0.5 parts of water (calculation basis from the 1:0.5 mixture of the ethyl cellulose dispersion) and mixed with the ethyl cellulose dispersion. The analgesic pellets are sprayed with the dispersion in a fluidized bed unit until the weight of the coated pellets reaches 110% of the weight of the uncoated pellets used.

Capsules
One hundred ten mg of coated emetic pellets and 165 mg of coated analgesic pellets are mixed per capsule and filled into size 1 hard gelatin capsules.

Example 23

Multiparticulate Form

Antagonist Pellets

Naloxone hydrochloride dihydrate	20 mg
Lactose	7 mg
Microcrystalline Cellulose PH101	20 mg
Hydroxypropyl cellulose with low degree of substitution (LH31, Shin-Etsu)	3 mg

All components are mixed intimately with one another for about 5 minutes in a suitable mixer. The mixture is granulated during mixing with such an amount of purified water that a moist

granulated mass is formed. The granules thus obtained are extruded in a Nica extruder through a die with 1-mm extrusion openings, rounded on a Spheronizer for 5 minutes, dried in a fluidized bed at 60°C, and screened by means of a 1.5-mm screen and a 0.5-mm screen.

Coating on Antagonist Pellets

Cellulose acetate containing 39.8% of acetate	9.5 mg
Macrogol 3350	0.5 mg
Titanium dioxide	0.5 mg

Quantity data per 100 mg of emetic pellets

Cellulose acetate and Macrogol are dissolved in an acetone-water mixture (95:5 parts by weight) to form a 3.8% solution, titanium dioxide is dispersed in the mixture, and the cores are sprayed with the suspension in a fluidized bed unit until the mass of the coated pallets reaches 110% of the weight of the uncoated pellets used.

Analgesic Pellets

0.5-mm nonpareils (sucrose-corn starch starter pellets, Werner)	50 mg
Morphine sulfate pentahydrate	60 mg
Povidone K 30	30 mg
Cayenne pepper	5 mg
Talc	10 mg

Morphine sulfate and Povidone are dissolved in purified water, and cayenne pepper and talc are dispersed in the solution. The suspension is sprayed on the nonpareils at 60°C and dried. The pellets are screened by means of a 1.5-mm screen and a 0.5-mm screen.

Coating on Analgesic Pellets

Ethyl cellulose dispersion (Aquacoat ECD 30, FMC Corporation)	10.0 mg
Glycerol monostearate	2.0 mg
Talc	2.0 mg
Titanium dioxide	1.0 mg

Quantity data per 150 mg of analgesic pellets; the weight of ethyl cellulose is stated as the dry weight from the 30% dispersion of the commercial product.

Ethyl cellulose dispersion is mixed with purified water at a ratio of 1:0.5, and glycerol monostearate is incorporated while stirring for at least two hours. Talc and titanium dioxide are dispersed in 0.5 parts of water (calculation basis from the 1:0.5 mixture of the ethyl cellulose dispersion) and mixed with the ethyl cellulose dispersion. The analgesic pellets are sprayed with the dispersion in a fluidized bed unit until the weight of the coated pellets reaches 110% of the weight of the uncoated pellets used.

Capsules

Fifty-five mg of coated antagonist pellets and 170 mg of coated analgesic pellets are mixed per capsule and filled into size 2 hard gelatin capsules.

Example 24

Dry coated tablets

Core

Emetine hydrochloride pentahydrate	60 mg
Hydrogenated castor oil (Cutina HR)	40 mg

Emetine hydrochloride pentahydrate and finely powdered hydrogenated castor oil are mixed and pressed into round, biconvex tablets with a diameter of 6.5 mm on a tabletting press.

Coating on Core

Cellulose acetate containing 39.8% of acetate	9.5 mg
Macrogol 3350	0.5 mg

The coating components are dissolved in an acetone-water mixture (95:5 parts by weight) to obtain a 3.8% solution and sprayed on the cores.

Dry coating

Morphine sulfate pentahydrate	60 mg
Methyl hydroxypropyl cellulose 100 000 m·Pas (Metolose 90 SH 100 000, Shinetsu)	100 mg
Microcrystalline cellulose (Avicel PH 102)	165 mg
Lactose monohydrate	164.9 mg
Capsaicin, micronized	0.1 mg
Magnesium stearate	5 mg
Colloidal silica	5 mg

All dry coating components were mixed, about 250 mg of the mixture were filled into the tablet die in a tabletting press with a mold for 13 mm biconvex tablets, the 6.5-mm core coated with cellulose acetate was inserted in a centered manner, the remaining 250 mg of the dry coating mixture were filled in, and the dry coating was pressed around the core.

Example 25

Oral Osmotic Therapeutic System (OROS)

Active Ingredient Layer

Morphine sulfate pentahydrate	125 mg
Macrogol 200 000	280 mg
Povidone (number-average molecular weight 40,000)	26 mg
Cayenne pepper	15 mg
Magnesium stearate	4 mg

Morphine sulfate and Macrogol are mixed in the dry state in a planetary mixer and subsequently kneaded into a moist mass while slowly adding a solution of the Povidone in 115 mg of ethyl alcohol, and this moist mass is then passed through a 0.8-mm screen. After drying for 24 hours at room temperature under an exhaust hood, the particles are screened together with the magnesium stearate and cayenne pepper through a 1.0-mm screen and mixed in a container mixer.

Push Layer

Methyl hydroxypropyl cellulose, 6 m·Pas	13 mg
Sodium chloride	80 mg
Macrogol 7 000 000	166 mg
Magnesium stearate	1 mg

Sodium chloride, Macrogol and half of the methyl hydroxypropyl cellulose are mixed in the dry state for 3 minutes in a fluidized-bed granulator and subsequently granulated and dried by spraying on a solution of the second half of the methyl hydroxypropyl cellulose in 75 mg while supplying warm air. The granular product is subsequently screened together with the magnesium stearate through a 2.5-mm screen in a Comil.

Emetic Layer

Emetine	50 mg
Hydrogenated castor oil (Cutina HR)	50 mg

Emetine and hydrogenated castor oil are prepressed into tablets weighing about 250 mg in a tabletting press with a 10-mm prepressing punch, The prepressed tablets are then subjected to size reduction by means of a breaker and a 1.0-mm screen.

Preparation of the Three-Layer Tablets

One hundred mg of the granular product of the emetic layer, 260 mg of the push layer and 450 mg of the active ingredient layer per tablet are filled one after another into the die of a suitable tabletting press and pressed into a three-layer tablet.

Coating on Core

Cellulose acetate containing 39.8% of acetate	38 mg
Macrogol 3350	2 mg

The coating components are dissolved in an acetone-water mixture (95:5 parts by weight) to form a 3.8% solution and sprayed on the cores. Two holes of 0.75 mm are drilled through the coating in order to connect the active ingredient layer with the external environment of the system.

Example 26

Oral Osmotic Therapeutic System

The procedure described in Example 25 is followed, with the difference that the emetic layer has

the following composition:

Emetine hydrochloride pentahydrate	60 mg
Hydrogenated castor oil (Cutina HR)	40 mg

Emetine hydrochloride pentahydrate and hydrogenated castor oil are prepressed into tablets weighing about 250 mg in a tabletting press with a 10-mm prepressing punch. The prepressed tablets are then subjected to size reduction by means of a breaker and a 1.0-mm screen.

All other manufacturing steps are carried out as described in Example 25.

Example 27

Dry coated tablets

Core

Natrexone hydrochloride	50 mg
Spray-dried lactose	46 mg
Magnesium stearate	2 mg
Colloidal silica	2 mg

All components are mixed and pressed into round, biconvex tablets with a diameter of 6.5 mm on a tabletting press.

Coating on Core

Cellulose acetate containing 39.8% of acetate	9.5 mg
Macrogol 3350	0.5 mg

The coating components are dissolved in an acetone-water mixture (95:5 parts by weight) and sprayed on the cores.

Dry coating

Morphine sulfate pentahydrate	60 mg
Methyl hydroxypropyl cellulose 100,000 m·Pas (Metolose 90 SH 100 000, Shinetsu)	100 mg
Xanthan, NF	40 mg
Microcrystalline cellulose (Avicel PH 102)	165 mg
Lactose monohydrate	155 mg
Cayenne pepper	10 mg
Magnesium stearate	5 mg
Colloidal silicate	5 mg

All dry coating components are mixed, about 270 mg of the mixture are filled into the tablet die

in a tabletting press with a mold for 13 mm biconvex tablets, the core coated with cellulose acetate is inserted in a centered manner, the remaining 270 mg of the dry coating mixture are filled in, and the dry coating is pressed around the core.

Example 28

Multiparticulate Form

Emetic Pellets

Emetine	50 mg
Lactose	15 mg
Microcrystalline cellulose PH 101	30 mg
Hydroxypropyl cellulose with low degree of substitution (LH31, Shin-Etsu)	5 mg

All components are mixed intimately with one another in a suitable mixer for about 5 minutes. The mixture is granulated during mixing with such an amount of purified water that a moist granulated mass is formed. The granules thus obtained are extruded in a Nica extruder through a die with 1-mm extrusion openings, rounded on a Spheronizer for 5 minutes, dried in a fluidized bed at 60°C, and screened by means of a 1.5-mm screen and a 0.5-mm screen.

Coating on Emetic Pellets

Cellulose acetate containing 39.8% of acetate	9.5 mg
Macrogol 3350	0.5 mg
Titanium dioxide	0.5 mg

Quantity data per 100 mg emetic pellets

Cellulose acetate and Macrogol are dissolved in an acetone-water mixture (95:5 parts by weight) to form a 3.8% solution, titanium dioxide is dispersed in the mixture, and the cores are sprayed with the suspension in a fluidized bed unit until the mass of the coated pallets reaches 110% of the weight of the uncoated pellets used.

Analgesic Pellets

0.5-mm nonpareils (sucrose-corn starch starter pellets, Werner)	50 mg
Morphine sulfate pentahydrate	60 mg
Povidone K 30	30 mg
Capsaicin	0.1 mg
Talc	9.9 mg
Xanthan	30 mg

Morphine sulfate and Povidone are dissolved in purified water and half of the talc is dispersed in the solution. Capsaicin is dissolved in ethyl alcohol to obtain a 10% solution, and the solution is added to the suspension. The suspension is sprayed on the rotating nonpareils at 55°C in a Rotogranulator (Glatt), and the xanthan is fed continuously into the mass of the moistened, rotating pellets as a powder mixed with the second half of the talc. After the conclusion of

drying, the pellets are screened by means of a 1.5-mm screen and a 0.5-mm screen.
Coating on Analgesic Pellets

Ethyl cellulose dispersion (Aquacoat ECD 30, FMC Corporation)	12.0 mg
Glycerol monostearate	2.4 mg
Talc	2.4 mg
Titanium dioxide	1.2 mg

Quantity data per 180 mg of analgesic pellets; the weight of ethyl cellulose is stated as the dry weight from the 30% dispersion of the commercial product.

Ethyl cellulose dispersion is mixed with purified water at a ratio of 1:0.5 and glycerol monostearate is incorporated while stirring for at least two hours. Talc and titanium dioxide are dispersed in 0.5 parts of water (calculation basis from the 1:0.5 mixture of the ethyl cellulose dispersion) and mixed with the ethyl cellulose dispersion. The analgesic pellets are sprayed with the dispersion in a fluidized bed unit until the weight of the coated pellets reaches 110% of the weight of the uncoated pellets used.

Capsules
One hundred ten mg of coated emetic pellets and 198 mg of coated analgesic pellets are mixed per capsule and filled into size 1 hard gelatin capsules.

Example 29

Multiparticulate Form

Emetic Pellets

Emetine	50 mg
Lactose	15 mg
Microcrystalline cellulose PH101	30 mg
Hydroxypropyl cellulose with low degree of substitution (LH31, Shin-Etsu)	5 mg

All components are mixed intimately with one another for about 5 minutes in a suitable mixer. The mixture is granulated during mixing with such an amount of purified water that a moist granulated mass is formed. The granules thus obtained are extruded in a Nica extruder through a die with 1-mm extrusion openings, rounded on a Spheronizer for 5 minutes, dried in a fluidized bed at 60°C, and screened by means of a 1.5-mm screen and a 0.5-mm screen.

Coating on Emetic Pellets

Cellulose acetate containing 39.8% of acetate	9.5 mg
Macrogol 3350	0.5 mg
Titanium dioxide	0.5 mg

Quantity data per 100 mg of emetic pellets

Cellulose acetate and Macrogol are dissolved in an acetone-water mixture (95:5 parts by weight) to form a 3.8% solution, titanium dioxide is dispersed in the mixture, and the cores are sprayed with the suspension in a fluidized bed unit until the mass of the coated pallets reaches 110% of

the weight of the uncoated pellets used.

Antagonist Pellets

Naloxone hydrochloride dihydrate	20 mg
Lactose	7 mg
Microcrystalline cellulose PH101	20 mg
Hydroxypropyl cellulose with low degree of substitution (LH31, Shin-Etsu)	3 mg

All components are mixed intimately with one another in a suitable mixer for about 5 minutes. The mixture is granulated during mixing with such an amount of purified water that a moist granulated mass is formed. The granules thus obtained are extruded in a Nica extruder through a die with 1-mm extrusion openings, rounded on a Spheronizer for 5 minutes, dried in a fluidized bed at 60°C, and screened by means of a 1.5-mm screen and a 0.5-mm screen.

Coating on Antagonist Pellets

Cellulose acetate containing 39.8% of acetate	4.75 mg
Macrogol 3350	0.25 mg
Titanium dioxide	0.25 mg

Quantity data per 50 mg of emetic pellets

Cellulose acetate and Macrogol are dissolved in an acetone-water mixture (95:5 parts by weight) to form a 3.8% solution, titanium dioxide is dispersed in the mixture, and the cores are sprayed with the suspension in a fluidized bed unit until the mass of the coated pallets reaches 110% of the weight of the uncoated pellets used.

Analgesic Pellets

0.5-mm nonpareils (sucrose-corn starch starter pellets, Werner)	50 mg
Morphine sulfate pentahydrate	60 mg
Povidone K 30	30 mg
Capsaicin	0.1 mg
Talc	9.9 mg
Xanthan	30 mg

Morphine sulfate and Povidone are dissolved in purified water and half of the talc is dispersed in the solution. Capsaicin is dissolved in ethyl alcohol to obtain a 10% solution, and the solution is added to the suspension. The suspension is sprayed on the rotating nonpareils at 55°C in a Rotogranulator (Glatt), and the xanthan is fed continuously into the mass of the moistened, rotating pellets as a powder mixed with the second half of the talc. After the conclusion of drying, the pellets are screened by means of a 1.5-mm screen and a 0.5-mm screen.

Coating on Analgesic Pellets

Ethyl cellulose dispersion (Aquacoat ECD 30, FMC Corporation)	12.0 mg
Glycerol monostearate	2.4 mg
Talc	2.4 mg

Titanium dioxide	1.2 mg

Quantity data per 180 mg of analgesic pellets; the weight of ethyl cellulose is stated as the dry weight from the 30% dispersion of the commercial product.

Ethyl cellulose dispersion is mixed with purified water at a ratio of 1:0.5 and glycerol monostearate is incorporated while stirring for at least two hours. Talc and titanium dioxide are dispersed in 0.5 parts of water (calculation basis from the 1:0.5 mixture of the ethyl cellulose dispersion) and mixed with the ethyl cellulose dispersion. The analgesic pellets are sprayed with the dispersion in a fluidized bed unit until the weight of the coated pellets reaches 110% of the weight of the uncoated pellets used.

Capsules

One hundred ten mg of coated emetic pellets, 55 mg of antagonist pellets and 198 mg of analgesic pellets per capsule are mixed with a gel-forming agent and filled into size 0 hard gelatin capsules.

Patent Claims:

1. Dosage form safeguarded from abuse, characterized in that in addition to one or more active ingredients that could be potentially subject to abuse, it contains two or more of the following components a)-d):

(a) at least one substance that irritates the nasal and/or pharyngeal region;

(b) at least one agent that increases the viscosity, which forms a gel in an extract obtained from the dosage form with the aid of a required minimum quantity of an aqueous liquid, wherein the said gel continues to be able to be visually distinguished after being introduced into an additional quantity of an aqueous liquid;

(c) at least one antagonist for the active ingredient or the active ingredients that could be potentially subject to abuse; and

(d) at least one emetic.

2. Dosage form in accordance with claim 1, characterized in that it contains three of the said components (a)-(d), preferably (a), (b) and (c) or (a), (b) and (d).

3. Dosage form in accordance with claim 1, characterized in that it contains all the components (a)-(d).

4. Dosage form in accordance with claim 1 or 2, containing two or three of the said components (a), (b) and (d), characterized in that the active ingredient is selected from the group comprising opiates, opioids, tranquilizers, stimulants and other narcotics.

5. Dosage form in accordance with claim 4, characterized in that the active ingredient is selected from the group comprising *N*-{1-[2-(4-ethyl-5-oxo-2-tetrazolin-1-yl)-ethyl]-4-methoxymethyl-4-piperidyl} propionanilide (alfentanil), 5,5-diallyl barbituric acid (allobarbital), allylprodine, alpha-prodine, 8-chloro-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-a][1,4]-benzodiazepine (alprazolam), 2-diethylaminopropiophenone (amfepramone), (±)-α-methyl phenethylamine (amphetamine), 2-(α-methylphenethyl-amino)-2-phenyl acetonitrile (amphetaminil), 5-ethyl-5-isopentyl barbituric acid (amobarbital), anileridine, apocodeine, 5,5-diethyl barbituric acid (barbital), benzylmorphine, bezitramide, 7-bromo-5-(2-pyridyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (bromazepam), 2-bromo-4-(2-chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*][1,2,4]-triazolo[4,3-a][1,4]diazepine (brotizolam), 17-cyclopropylmethyl-4,5α-epoxy-7α[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6-methoxy-6,14-*endo*-ethanomorphinan-3-ol (buprenorphine), 5-butyl-5-ethyl barbituric acid (butobarbital), butorphanol, (7-chloro-1,3-dihydro-1-methyl-2-oxo-5-phenyl-2*H*-1,4-benzodiazepin-3-yl)-dimethyl carbamate (camazepam), (1*S*,2*S*)-2-amino-1-phenyl-1-propanol (cathine/D-norpseudoephedrine), 7-chloro-*N*-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2-ylamine-4 oxide (chlordiazepoxide), 7-chloro-1-methyl-5-phenyl-1*H*-1,5-benzodiazepine-2,4(3*H*,5*H*)-dione (clobazam), 5-(2-chlorophenyl)-7-nitro-1*H*-1,4-benzodiazepin-2(3*H*)-one (clonazepam), clonitazene, 7-chloro-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-3-carboxylic acid (clorazepate), 5-(2-chlorophenyl)-7-ethyl-1-methyl-1*H*-thieno[2,3-e][1,4]-diazepin-2(3*H*)-one (clotiazepam), 10-chloro-11b-(2-

chlorophenyl)-2,3,7,11b-tetrahydrooxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one (cloxazolam), (-)-methyl-[3β-benzoyloxy-2β(1αH,5α*H*)-tropane carboxylate (cocaine), 4,5α-epoxy-3-methoxy-17-methyl-7-morphinen-6α-ol (codeine), 5-(1-cyclohexenyl)-5-ethyl barbituric acid (cyclobarbital), cyclorphan, cyprenorphine, 7-chloro-5-(2-chlorophenyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (delorazepam), desomorphine, dextromoramide, (+)-(1-benzyl-3-dimethylamino-2-methyl-1-phenylpropyl) propionate (dextropropoxyphene), dezocine, diampromide, diamorphone, 7-chloro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (diazepam), 4,5α-epoxy-3-methoxy-17-methyl-6α-morphinanol (dihydyrocodeine), 4,5[?]-epoxy-17-methyl-3,6a-morphinandiol (dihydromorphine), dimenoxadol, dimephetamol [sic - Tr.Ed.], dimethyl thiambutene, dioxaphetyl butyrate, dipipanone, (6*aR*,10*aR*)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[c]chromen-1-ol (dronabinol), eptazocine, 8-chloro-6-phenyl-4*H*-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine (estazolam), ethoheptazine, ethyl methyl thiambutene, ethyl-[7-chloro-5-(2-fluorophenyl)-2,3-dihydro-2-oxo-1*H*-1,4-benzodiazepin-3-carboxylate] (ethyl loflazepate), 4,5[?]-epoxy-3-ethoxy-17-methyl-7-morphinen-6[?]-ol (ethylmorphine), etonitrazene, 4,5α-epoxy-7α-(1-hydroxy-1-methylbutyl)-6-methoxy-17-methyl-6,14-*endo*-etheno-morphinan-3-ol (etorphine), *N*-ethyl-3-phenyl-8,9,10-trinorbornan-2-ylamine (fencamfamine), 7-[2-(α-methylphenethyl-amino)-ethyl] theophylline (fenethylline), 3-(α-methylphenethylamino) propionitrile (fenproporex), *N*-(1-phenethyl-4-piperidyl) propionanilide (fentanyl), 7-chloro-5-(2-fluorophenyl)-1-methyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (fludiazepam), 5-(2-fluorophenyl)-1-methyl-7-nitro-1*H*-1,4-benzodiazepin-2-(3*H*)-one (flunitrazepam), 7-chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (flurazepam), 7-chloro-5-phenyl-1-(2,2,2-trifluoroethyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (halazepam), 10-bromo-11b-(2-fluorophenyl)-2,3,7,11b-tetrahydro[1,3]oxazolo[3,2-d][1,4]benzodiazepin-6(5*H*)-one (haloxazolam), heroin, 4,5α-epoxy-3-methoxy-17-methyl-6-morphinanone (hydrocodone), 4,5α-epoxy-3-hydroxy-17-methyl-6-morphinanone (hydromorphone), hydroxypethidine, isomethadone, hydroxymethyl morphinan, 11-chloro-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4*H*-[1,3]oxazino[3,2-d][1,4]benzodiazepin-4,7(6*H*)-dione (ketazolam), 1-[4-(3-hydroxyphenyl)-1-methyl-4-piperidyl]-1-propanone (ketobemidone), (3*S*,6*S*)-6-dimethylamino-4,4-diphenylheptan-3-yl acetate (levacetylmethadol (LAAM)), (-)-6-dimethylamino-4,4-diphenyl-3-heptanone (levomethadone), (-)-17-methyl-3-morphinanol (levorphanol), levophenacyl morphan, lofentanil, 6-(2-chlorophenyl)-2-(4-methyl-1-piperazinylmethylene)-8-nitro-2*H*-imidazo[1,2a][1,4]benzodiazepin-1(4*H*)-one (loprazolam), 7-chloro-5-(2-chlorophenyl)-3-hydroxy-1*H*-1,4-benzodiazepin-2(3*H*)-one (lorazepam), 7-chloro-5-(2-chlorophenyl)-3-hydroxy-1-methyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (lormetazepam), 5-(4-chlorophenyl)-2,5-dihydro-3*H*-imidazo[2,1-*a*]isoindol-5-ol (mazindol), 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (medazepam), *N*-(3-chloropropyl)-α-methylphenetylamine (mefenorex), meperidine, 2-methyl-2-propyl trimethylene dicarbamate (meprobamate), meptazinol, metazocine, methylmorphine, *N*,α-dimethylphenetylamine (methamphetamine), (±)-6-dimethylamino-4,4-diphenyl-3-heptanone (methadone), 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone (methaqualone), methyl-[2-phenyl-2-(2-piperidyl)acetate] (methyl phenidate), 5-ethyl-1-methyl-5-phenyl barbituric acid (methyl phenobarbital), 3,3-diethyl-5-methyl-2,4-piperidinedione (methyprylon), metopon, 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (midazolam), 2-(benzhydrylsulfinyl) acetamide (modafinil), 4,5α-epoxy-17-methyl-7-morphinene-3,6α-diol (morphine), myrophine, (±)-*trans*-3-(1,1-dimethylheptyl)-7,8,10,10α-tetrahydro-1-hydroxy-6,6-dimethyl-6*H*-

dibenzo[*b*,*d*]pyran-9(6α*H*)-one (nabilone), nalbuphen, nalorphine, narceine, nicomorphine, 1-methyl-7-nitro-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (nimetazepam), 7-nitro-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (nitrazepam), 7-chloro-5-phenyl-1*H*-1,4-benzodiazepin-2-(3*H*)-one (nordazepam), norlevorphanol, 6-dimethylamino-4,4-diphenyl-3-hexanone (normethadone), normorphine, norpipanone, the coagulated juice of the plants belonging to the species *Papaver somniferum* (opium), 7-chloro-3-hydroxy-5-phenyl-1*H*-1,4-benzodiazepin-2-(3*H*)-one (oxazepam), (*cis-trans*)-10-chloro-2,3,7,11b-tetrahydro-2-methyl-11b-phenyloxazolo[3,2-*d*][1,4]benzodiazepin-6-(5*H*)-one (oxazolam), 4,5α-epoxy-14-hydroxy-3-methoxy-17-methyl-6-morphinanone (oxycodone), oxymorphone, plants and plant parts of the plants belonging to the species *Papaver somniferum* (including the subspecies *setigerum*) (*Papaver somniferum*), papaveretum, 2-imino-5-phenyl-4-oxazolidinone (pernoline), 1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol (pentazocine), 5-ethyl-5-(1-methylbutyl) barbituric acid (pentobarbital), ethyl-(1-methyl-4-phenyl-4-piperidine-carboxylate) (pethidine), phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, pholcodeine, 3-methyl-2-phenyl morpholine (phenmetrazine), 5-ethyl-5-phenyl barbituric acid (phenobarbital), α,α-dimethyl phenethylamine (phentermine), 7-chloro-5-phenyl-1-(2-propinyl)-1*H*-1,4-benzodiazepin-2(3*H*)-one (pinazepam), α-(2-piperidyl)benzhydryl alcohol (pipradol), 1'-(3-cyano-3,3-diphenylpropyl)[1,4'-bipiperidine]-4'-carboxamide (piritramide), 7-chloro-1-(cyclopropylmethyl)-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (prazepam), profadol, proheptazine, promedol, properidine, propoxyphene, *N*-(1-methyl-2-piperidinoethyl)-*N*-(2-pyridyl) propionamide, methyl-{3-[4-methoxycarbonyl-4-(*N*-phenylpropaneamido)piperidino]propanoate} (remifentanil), 5-*sec.*-butyl-5-ethyl barbituric acid (secbutabarbital), 5-allyl-5-(1-methylbutyl) barbituric acid (secobarbital), *N*-{4-methoxymethyl-1-[2-(2-thienyl)ethyl]-4-piperidyl} propionanilide (sufentanil), 7-chloro-2-hydroxy-methyl-5-phenyl-1*H*-1,4-benzodiazepin-2-(3*H*)-one (temazepam), 7-chloro-5-(1-cyclohexenyl)-1-methyl-1*H*-1,4-benzodiazepin-2(3*H*)-one (tetrazepam), ethyl-(2-dimethylamino-1-phenyl-3-cyclohexane-1-carboxylate) (tilidine (*cis* and *trans*)), tramadol, 8-chloro-6-(2-chlorophenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine (triazolam), 5-(1-methylbutyl)-5-vinyl barbituric acid (vinylbital), (1R*,2R*)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl) phenol, (1R,2R,4S)-2-[dimethylamino)methyl-4-(*p*-fluorobenzyloxy)-1-(*m*-methoxyphenyl) cyclohexanol, each optionally in the form of corresponding stereoisomeric compounds as well as corresponding derivatives, especially esters or ethers, and all being physiologically compatible compounds, especially salts and solvates.

6. Dosage form in accordance with one of the claims 1 through 3, containing the said component (c), characterized in that the active ingredient is selected from the group comprising the opiates, opioids, stimulants and other narcotics.

7. Dosage form in accordance with claim 6, characterized in that the active ingredient has been selected from the group comprising *N*-{1-[2-(4-ethyl-5-oxo-2-tetrazolin-1-yl)ethyl]-4-methoxymethyl-4-piperidyl} propionanilide (alfentanil), allylprodine, alpha-prodine, 2-diethylaminopropiophenone (amfepramone), (±)-α-methyl phenethylamine (amphetamine), 2-(α-methylphenethylamino)-2-phenyl acetonitrile (amphetaminil), anileridine, apocodeine, benzylmorphine, bezitramide, 17-cyclopropylmethyl-4,5α-epoxy-7α[(S)-1-hydroxy-1,2,2-trimethyl-propyl]-6-methoxy-6,14-*endo*-ethanomorphinan-3-ol (buprenorphine), butorphanol, (1*S*,2*S*)-2-amino-1-phenyl-1-propanol (cathine/D-norpseudoephedrine), clonitazene, (-)-methyl-[3β-benzoyloxy-2β(1αH,5α*H*)-propane-

carboxylate] (cocaine), 4,5α-epoxy-3-methoxy-17-methyl-7-morphinen-6α-ol, cyclorphan, cyprenorphine, desmorphine, dextromoramide, (+)-(1-benzyl-3-dimethylamino-2-methyl-1-phenylpropyl) propionate (dextropropoxyphene). dezocine, diampromide, diamorphone, 4,5α-epoxy-3-methoxy-17-methyl-6α-morphinanol (dihydrocodeine), 4,5[?]-epoxy-17-methyl-3,6a-morphinandiol (dihydromorphine), dimenoxadol, dimephetamol, dimethyl thiambutene, dioxaphetyl butyrate, dipipanone, (6a*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[c]chromen-1-ol (dronabinol), eptazocine, ethoheptazine, ethyl methyl thiambutene, 4,5[?]-epoxy-3-ethoxy-17-methyl-7-morphinen-6[?]-ol (ethylmorphine), etonitazene, 4,5α-epoxy-7α-(1-hydroxy-1-methylbutyl)-6-methoxy-17-methyl-6,14-*endo*-etheno-morphinan-3-ol (etorphine), *N*-ethyl-3-phenyl-8,9,10-trinorbornan-2-ylamine (fencamfamine), 7-[2-(α-methylphenethylamino)-ethyl] theophylline (fenethylline), 3-(α-methylphenethylamino) propionitrile (fenproporex), *N*-(1-phenetyl-4-piperidyl) propionanilide (fentanyl), heroin, 4,5α-epoxy-3-methoxy-17-methyl-6-morphinanone (hydrocodone), 4,5α-epoxy-3-hydroxy-17-methyl-6-morphinanone (hydromorphone), hydroxypethidine, isomethadone, hydroxymethyl morphinan, 1-[4-(3-hydroxyphenyl)-1-methyl-4-piperidyl]-1-propanone (ketobemidone), (3*S*,6*S*)-6-dimethylamino-4,4-diphenylheptan-3-yl acetate (levacetylmethadol (LAAM)), (-)-6-dimethylamino-4,4-diphenyl-3-heptanone (levomethadone), (-)-17-methyl-3-morphinanol (levorphanol), levophenacyl morphan, lofentanil, 5-(4-chlorophenyl)-2,5-dihydro-3*H*-imidazo[2,1-*a*]isoindol-5-ol (mazindol), *N*-(3-chloropropyl)-α-methylphenetylamine (mefenorex), meperidine, meptazinol, metazocine, methylmorphine, *N*,α-dimethyl phenethylamine (methamphetamine), (±)-6-dimethylamino-4,4-diphenyl-3-heptanone (methadone), methyl-[2-phenyl-2-(2-piperidyl)acetate] (methyl phenidate), 3,3-diethyl-5-methyl-2,4-piperidinedione (methyprylone), 2-(benzhydrylsulfinyl) acetamide (modafinil), 4,5α-epoxy-17-methyl-7-morphinene-3,6α-diol (morphine), myrophine, (±)-*trans*-3-(1,1-dimethylheptyl)-7,8,10,10α-tetrahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo[*b,d*]pyran-9(α*H*)-one (nabilone), nalbuphen, narceine, nicomorphine, norlevorphanol, 6-dimethylamino-4,4-diphenyl-3-hexanone (normethadone), normorphine, norpipanone, the coagulated juice of the plants belonging to the species *Papaver somniferum* (opium), 4,5α-epoxy-14-hydroxy-3-methoxy-17-methyl-6-morphinanone (oxycodone), oxymorphone, plants and plant parts of the plants belonging to the species *Papaver somniferum* (including the subspecies *setigerum*) (*Papaver somniferum*), papaveretum, 2-imino-5-phenyl-4-oxazolidinone (pernoline), 1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol (pentazocine), ethyl-(1-methyl-4-phenyl-4-piperidine-carboxylate) (pethidine), phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, pholcodeine, 3-methyl-2-phenylmorpholine (phenmetrazine), α,α-dimethylphenetylamine (phentermine), α-(2-piperidyl)benzhydryl alcohol (pipradol), 1'-(3-cyano-3,3-diphenylpropyl)[1,4'-bipiperidine]-4'-carboxamide (piritramide), profadol, proheptazine, promedol, properidine, propoxyphene, *N*-(1-methyl-2-piperidinoethyl)-*N*-(2-pyridyl) propionamide, methyl{3-[4-methoxycarbonyl-4-(*N*-phenylpropanamido)-piperidino]propanoate} (remifentanil), *N*-(4-methoxymethyl-1-[2-(2-thienyl)ethyl]-4-piperidyl}propionanilide (sufentanil), ethyl-(2-dimethylamino-1-phenyl-3-cyclohexene-1-carboxylate) (tilidine (*cis* and *trans*)), tramadol, (1R*,2R*)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl) phenol, (1R,2R,4S)-2-[dimethylamino)methyl-4-(*p*-fluorobenzyloxy)-1-(*m*-methoxyphenyl) cyclohexanol, each optionally in the form of corresponding stereoisomeric compounds as well as corresponding derivatives, especially esters or ethers, and all being physiologically compatible compounds, especially salts and solvates.

8. Dosage form in accordance with one of the claims 4 through 7, characterized in that it contains one or more stimulants selected from the group comprising amphetamine, norpseudoephedrine, methyl phenidate and optionally the corresponding physiologically compatible compounds thereof, especially bases, salts and solvates thereof.

9. Dosage form in accordance with one of the claims 1 through 8, characterized in that the irritating substance of component (a) causes burning, itching, an urge to sneeze, increased production of secretion or a combination of at least two of these irritations.

10. Dosage form in accordance with one of the claims 1 through 9, characterized in that the irritating substance of component (a) is based on one or more constituents of at least one pungent drug.

11. Dosage form in accordance with claim 10, characterized in that the pungent drug is selected from the group comprising allii sativi bulbus, asari rhizoma c. herba, calami rhizoma, capsici fructus (paprika), capsici fructus acer (cayenne pepper), curcumae longae rhizoma, curcumae xanthorrhizae rhizoma, galangae rhizoma, myristicae semen, piperis nigri fructus (pepper), sinapis albae (erucae) semen, sinapis nigri semen, zedoariae rhizoma and zingiberis rhizoma, especially preferably from the group comprising capsici fructus (paprika), capsici fructus acer (cayenne pepper) and piperis nigri fructus (pepper).

12. Dosage form in accordance with claim 10 or 11, characterized in that the constituent is an *o*-methoxy(methyl) phenol compound, an acid amide compound, a mustard oil or a sulfide compound or is derived from such a compound.

13. Dosage form in accordance with one of the claims 10 through 12, characterized in that the constituent is selected from the group comprising myristicin, elemicin, isoeugenol, [?]-asarone, saffrole, gingerols, xanthorrhizol, capsaicinoids, preferably capsaicin, piperine, preferably *trans*-piperine, glucosinolates, preferably those based on nonvolatile mustard oils, especially preferably based on *p*-hydroxybenzyl mustard oil, methyl mercapto mustard oil or methyl sulfonyl mustard oil, and compounds derived from these constituents.

14. Dosage form in accordance with one of the claims 1 through 13, characterized in that component (b) has one or more viscosity-increasing agents selected from the group comprising microcrystalline cellulose containing 11 wt.% of carboxymethyl cellulose sodium (Avicel® RC 591), carboxymethyl cellulose sodium (Blanose®, CMC-Na C300 P®, Frimulsion BLC-5®, Tylose C300 P®), polyacrylic acid (Carbopol® 980 NF, Carbopol® 981), carob bean powder (Cesagum® LA-200, Cesagum® LID/150, Cesagum® LN-1), citrus pectin (Cesapectin® HM Medium Rapid Set), waxy corn starch (C®Gel 04201®), sodium alginate (Frimulsion ALG (E401)®), guar gum powder (Frimulsion BM®, Polygum 26/1-75®), Iota-carragheen (Frimulsion D021®), karaya gum, gellan gum (Kelcogel®, Kelcogel LT100®), galactomannan (Meyprogat 150®), tara seed powder (Polygum 43/1®), propylene glycol alginate (Protanal-Ester SD-LB®), apple pectin, pectin from lemon peel, sodium hyaluronate, tragacanth, tara gum (Vidogum SP 200®), fermented polysaccharide Welan Gum (K1A96) and xanthan gum (Xantural 180®).

15. Dosage form in accordance with one of the claims 1 through 14, characterized in that it contains the viscosity-increasing agent in an amount of $\geq$ 5 mg per dosage form, i.e., per dosage unit.

16. Dosage form in accordance with one of the claims 7 through 15, characterized in that an opiate or opioid antagonist, selected from the group comprising naloxone, naltrexone, nalmefene, nalid, nalmexone, nalorphine, naluphine, and respective corresponding physiologically compatible compounds, especially bases, salts and solvates, is used as the antagonist of component (c).

17. Dosage form in accordance with one of the claims 4 through 16, characterized in that a neuroleptic, selected from the group comprising haloperidol, promethazine, fluophenozine, perphenazine, levomepromazine, thioridazine, perazine, chlorpromazine, chlorprotheaxine [sic - chlorprothixene? - Tr.Ed.], zuclopenthixol, flupenthixol, prithipendyl, zotepine, penperidol, piparmerone, melperol and bromperidol is used as the antagonist of component (c) for a stimulant.

18. Dosage form in accordance with one of the claims 1 through 17, characterized in that the emetic of component (d) is based on one or more constituents of radix ipecacuanhae (ipecac), preferably on the constituent emetine, and/or apomorphine.

19. Dosage form in accordance with one of the claims 1 through 18, characterized in that the active ingredient or the active ingredients of component (c) and/or (d) is/are separated in space, wherein the active ingredient or the active ingredients being preferably located in at least one subunit (A) and component (c) and/or (d) being located in at least one subunit (B) and the components (c) and/or (d) from subunit (B) do not exert their action in the body in case of administration of the dosage form as intended.

20. Dosage form in accordance with claim 19, characterized in that both of the subunits (A) and (B) occur in the multiparticulate form, preferably in the form of microtablets, microcapsules, micropellets, granules, spheroids, beads or pellets, optionally pressed into tablets, filled into capsules or suspended in a liquid or a gel, the same form, i.e., shape being selected for both the subunit (A) and the subunit (B).

21. Dosage form in accordance with claim 20, characterized in that the forms of the subunits (A) and (B), which are shaped extensively identically, cannot be distinguished even visually.

22. Dosage form in accordance with claim 19, characterized in that the subunits (A) and (B) are arranged in the form of layers in relation to one another.

23. Dosage form in accordance with claim 22, characterized in that the layer-like subunits (A) and (B) are arranged vertically or horizontally in relation to one another.

24. Dosage form in accordance with claim 22, characterized in that subunit (B) forms a core, which is completely enveloped by the subunit (A).

25. Dosage form in accordance with claim 22, characterized in that subunit (A) forms a core, which is enveloped by subunit (B), the said envelope having at least one canal, which leads from the core to the surface of the dosage form.

26. Dosage form in accordance with one of the claims 22 through 25, characterized in that at least one, optionally swellable separating layer (C) is arranged between the layers of the subunits (A) and (B).

27. Dosage form in accordance with claim 22 or 26, characterized in that it is in the form of a tablet.

28. Dosage form in accordance with one of the claims 22, 23, 26 or 27, characterized in that the free surface of the subunit (B) is coated completely with at least one barrier layer (D) preventing the release of component (c) and/or (d) and optionally at least part of the free surface of subunit (A) and optionally at least part of the free surface of the separating layer (C) is coated with such a barrier layer.

29. Dosage form in accordance with one of the claims 22, 23, 26 or 27, characterized in that it has a push layer (P) between the subunits (A) and (B) and all free surfaces of the layer structure comprising the subunits (A) and (B), the push layer (P) and and [sic - Tr.Ed.] optionally the separating layer (C) are provided with a semipermeable coating (E), which is permeable to the releasing medium and is essentially impermeable to the active ingredient and to the components (c) and/or (d), and wherein the said coating (E) has at least one opening for releasing the active ingredient.

30. Dosage form in accordance with claim 19, characterized in that the subunit (A) has the form of a tablet, whose web and optionally one of the two bases are covered with at least one barrier layer (D) containing the emetic.

31. Dosage form in accordance with one of the claims 1 through 30, characterized in that it contains at least one active ingredient at least partially in the sustained-release form.

32. Dosage form in accordance with one of the claims 1 through 31 for oral administration.

33. Dosage form in accordance with claim 32, characterized in that it has at least one enteric coating.

34. Dosage form in accordance with one of the claims 19 through 33, characterized in that it contain [sic - Tr.Ed.] the component (a) and/or (b) in at least one subunit A and/or at least one subunit B.